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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

Memorandum

Date: 9-August-2002

Subject: Glufosinate Ammonium (PC Code 128850). Section 3 Registrations for Transgenic Cotton and Cotton (ID# - 0F06140), Transgenic Rice (ID# - 0F06210), and Bushberry (ID# - 2E06404). **Human Health Risk Assessment.** DP Barcodes: D274674, D274675, and D280452. Case Numbers: 292945, 293386, and 294699. Submission: S596736, S596735, and S609042. 40 CFR 180.473.

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Registration Division (7505C)

Aventis requested a Section 3 registration for application of glufosinate ammonium (butanoic acid, 2-amino-4-(hydroxymethylphosphinyl)-, monoammnoium salt) to transgenic rice, transgenic cotton, and cotton and the Interregional Research Project Number 4 (IR-4) requested a Section 3 registration for application of glufosinate ammonium to the bushberry crop subgroup. A summary of the human health risk resulting from the requested and registered uses of glufosinate ammonium is provided in this document. The hazard assessment was provided by PV Shah, Ph.D., of RAB1; the residue chemistry assessment, dietary exposure assessment, an aggregate risk assessments were provided by Tom Bloem of RAB1; the occupational and residential risk assessments were provided by Troy Swackhammer of RAB1; and the water exposure assessment was provided by John Ravenscroft of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Background: Technical glufosinate ammonium is a racemic mixture of the D and L enantiomers; only the L enantiomer is herbicidally active. The compound is a non-selective herbicide and acts as an inhibitor of glutamine synthetase which leads to poisoning of the plant by ammonia. Glufosinate ammonium is currently registered for use on both transgenic and nontransgenic crops. The transgenic plants currently registered (canola, sugar beet, corn, soybean) and the transgenic plants requested for registration (rice and cotton) have been engineered to express phosphiothrion-acetyl-transferase (PAT) which enables the plant to metabolize glufosinate ammonium into N-acetyl-glufosinate.

Current registrations include broadcast application to apple, grape, banana, potato (vine desiccant), and tree nut orchards with tolerances for the combined residues of glufosinate ammonium and 3-methylphosphonic propionic acid (HOE 061517; both expressed as glufosinate free acid equivalents) ranging from 0.05 - 0.80 ppm (40 CFR 180.473; see attachment 1 for structures). Glufosinate ammonium is also registered for application to the transgenic varieties of field corn, canola, sugar beet, and soybean with tolerances for the combined residues of glufosinate ammonium, 2-acetamido-4-methylphosphinico butanoic acid, and 3-methylphosphonic propionic acid (all expressed as glufosinate free acid equivalents) ranging from 0.2 - 25.0 ppm. Tolerances are also established for the combined residues of glufosinate ammonium and 3-methylphosphonic propionic acid (both expressed as glufosinate free acid equivalents) as a result of secondary residues in milk, eggs, and the meat, fat and meat byproducts of ruminants and poultry ranging from 0.02 ppm - 0.10 ppm. Glufosinate ammonium is also registered for lawn renovation purposes and as a spot treatment around ornamentals.

The petitioners are requesting a Section 3 registration for application of glufosinate ammonium to transgenic rice, transgenic cotton, cotton, and the bushberry crop subgroup and establishment of the following permanent tolerances for the combined residues of glufosinate ammonium (butanoic acid, 2-amino-4-(hydroxymethylphosphinyl)-, monoammonium salt), 2-acetamido-4-methylphosphinico-butanoic acid, and 3-methylphosphinico-propionic acid expressed as glufosinate ammonium free acid equivalents (proposed tolerance expression for the bushberry crop subgroup includes only glufosinate ammonium and 3-methylphosphinico-propionic acid):

rice, grain	1.0 ppm
rice, straw	1.6 ppm
cotton, undelinted seed	3.5 ppm
cotton, gin byproducts	12 ppm
bushberry crop subgroup 13b	0.10 ppm

Hazard Assessment: Glufosinate ammonium is toxicity category III for acute oral, dermal, and inhalation toxicities. It is toxicity category II for eye irritation. It is neither a dermal irritant nor a dermal sensitizer. For subchronic toxicity, the primary effects in the mouse were increased liver and kidney weights with increases in serum aspartate amino transferase and alkaline phosphatase. Signs of neurotoxicity were observed in rats in subchronic studies, such as aggressive behavior, piloerection, high startle response, and increased incidence of fearfulness.

In the chronic studies in the rat, increased mortality, increased occurrence of retinal atrophy, and inhibition of brain glutamine synthetase were observed, as were increased liver and kidney weights. In the mouse, increased mortality was observed, as were changes in glucose levels consistent with changes in glutathione levels. Increased mortality and electrocardiogram (EKG) alterations were observed in

dogs. There was no evidence of a treatment-related increase in tumors.
The developmental toxicity study in the rat produced dilated renal pelvis and/or hydroureter in the offspring at levels that produced significant increases in hyperactivity and vaginal bleeding in dams. Therefore, there was no qualitative or quantitative evidence of increased susceptibility following *in utero* exposure in the prenatal developmental study in rats. There was evidence of qualitative increased susceptibility in the rabbit developmental study. Decreased fetal body weight and increased mortality observed at 20 mg/kg/day is considered more severe than the effects seen in rabbit dams which included decreased food consumption, body weight, and body weight gain were observed at 20 mg/kg/day.

The reproductive toxicity study in rats indicated postnatal developmental toxicity at the highest dose tested (HDT) in the form of decrease in viable pups. No parental toxicity was seen at the HDT. Since developmental effects were observed in the absence of parental toxicity, there is evidence of quantitative increased susceptibility in offspring.

A consistent pattern of neurotoxicity was seen in several studies, including the subchronic, developmental, and chronic studies in rats, mice, and dogs. In addition to the clinical signs such as hyperactivity, aggressive behavior, tono-clonic convulsion, piloerection, and high startle response, retinal atrophy was also observed. Changes in glutamine synthetase levels were observed in liver, kidney, and brain in rats. The HED Hazard Identification Assessment Review Committee (HIARC) concluded that the changes in liver and kidney glutamine synthetase activity and changes in liver and kidney weights were an adaptive response and not an adverse effect. The HIARC also concluded that the changes in brain glutamine synthetase activity are of significant concern. It is expected that the requested special studies will provide the information needed to confirm these conclusions and allow further characterize of these effects.

There is no concern for mutagenic activity in several studies including: Salmonella E. Coli, *in vitro* mammalian cell gene mutation assays, mammalian cell chromosome aberration assays, *in vivo* mouse bone marrow micronucleus assays, and unscheduled DNA synthesis assays.

A rat metabolism study with dermal application indicated that about 50% of the administered radioactivity was absorbed 48 hours after a single dose application. In oral metabolism studies, it was shown that over 80% of administered radioactivity is excreted within 24 to 48 hours as the parent compound in the feces and kidneys. In the urine, two metabolites (HOE 061517 and HOE 086486) were identified in minor amounts. In the feces, two additional metabolites (HOE 099730 and HOE 042231) were detected in minor amounts. Highest tissue levels were found in liver, kidney, and gonads.

Additional testing was conducted with HOE 061517 and HOE 099730 (metabolites of glufosinate ammonium) as well as with the L-isomer of glufosinate ammonium (HOE 058192). These compounds, tested in subchronic rat, mouse, and dog studies, and in developmental toxicity studies in rat and rabbit, showed a similar toxicity profile as the parent compound (HOE 039866).

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision: The HIARC met on June 4, 2002 and June 11, 2002 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to glufosinate ammonium (TXR No.

0050900). The HIARC determined that a 3x database uncertainty factor, due to the lack of a study that measures glutamine synthetase activity in the young and adult animals, should be applied to all dietary and residential dermal, inhalation, and incidental oral exposure assessments. The HIARC also determined that for occupational and residential inhalation exposure assessments an additional 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. The FQPA SFC met on July 8, 2002 and determined that reliable data demonstrate that the safety of infants and children will be protected by use of the 3x (residential dermal, incidental oral, and dietary) and 30x (residential inhalation) database uncertainty factors set by HIARC; therefore, the special FQPA SF should be reduced to 1x (TXR No. 0050964).

Risk assessments were conducted for the specific exposure scenarios listed below. The acute and chronic reference doses were calculated by dividing the respective no observable adverse effect level (NOAEL) by 300 (3x database uncertainty factor for lack of a study that measures glutamine synthetase in the young and adult animals, 10x for interspecies extrapolation, and 10x for intraspecies variation). Since the special FQPA SF has been reduced to 1x, the acute and chronic population adjusted doses (aPAD and cPAD) are equal to the acute and chronic reference doses (RfDs). Based on the decisions made by the HIARC and the FQPA SFC, the level of concern for residential dermal, incidental oral, and residential inhalation exposures are 300, 300, and 3000, respectively, and the level of concern for occupational dermal and inhalation exposure are 100 and 1000, respectively. Glufosinate ammonium is classified as "not likely to be carcinogenic to humans" by all relevant routes of exposure based on adequate studies in two animal species. Therefore, a cancer risk assessment is not required. Since oral studies were selected for all durations of dermal and inhalation exposure, a 50% dermal absorption factor and a 100% inhalation absorption factor are used in the route-to-route extrapolation. Short-term oral, dermal, and inhalation exposures can be combined due to same toxicity end points.

acute dietary (Females 13-50 only)	NOAEL = 6.3 mg/kg/day	acute RfD and cPAD = 0.021 mg/kg/day
chronic dietary	NOAEL = 6.0 mg/kg/day	chronic RfD and cPAD = 0.02 mg/kg/day
short-term dermal	oral NOAEL = 6.3 mg/kg/day	Target MOE = 100 (occupational) 300 (residential)
short-term inhalation	oral NOAEL = 6.3 mg/kg/day	Target MOE = 1000 (occupational) 3000 (residential)
short-term incidental oral	oral NOAEL = 6.3mg/kg/day	Target MOE = 300 (residential exposure)
cancer	not likely to be a carcinogen	

Occupational Exposures and Risk Estimates: Pesticide handlers supporting and conduction applications to cotton, rice, and bushberries are anticipated to have short-term dermal and inhalation exposures. The aggregate risk index (ARI) approach was used to assess the combined risk of dermal and inhalation exposures, since HIARC selected the same toxicological endpoint for each route of exposure, but selected different target MOEs for each route. HED's level of concern is for ARIs <1. ARIs for handlers performing mixing/loading activities to support aerial applications on cotton and rice at the baseline level (no gloves) were 0.0041 and with label-required personal protective equipment (PPE) plus a dust-mist respirator were 0.64; both scenarios exceeded HED's level of concern. When handlers use closed mixing/loading systems to support aerial applications to cotton and rice, the corresponding ARI's are 1.2 and 1.4, respectively, and do not exceed HED's level of concern. Therefore, a revised Section B indicating aerial application to cotton and rice may only be made with closed mixing/loading systems is requested. ARI's for aerial applicators, flaggers, and groundboom applicators on cotton and rice were greater than 1 at the baseline level. ARI's for handlers supporting and performing applications to

bushberry were greater than 1 with label-required PPE.

For agricultural workers entering treated fields, anticipated post-application activities that will result in short-term dermal exposures comprise scouting in rice and cotton crops, with scouting in cotton crops representing the highest exposure potential due to a higher application rate for cotton (HED's level of concern is for occupational dermal MOEs <100). Workers performing cultural activities in bushberry fields are not anticipated to have appreciable post-application exposures, since the proposed label directs handlers to apply a directed spray to target weeds and avoid contacting the bushberry crop. The MOE for workers entering treated cotton crops is 810 on the day of treatment and does not exceed HED's level of concern. Post-application exposure for workers entering treated rice and bushberry fields are expected to be lower than estimated for workers entering treated cotton fields.

Residential Exposure and Risk Estimates: HED conducted an updated residential assessment for the lawn renovation (broadcast) and spot treatment registrations (see D258145, M. Christian, 7-Sep-1999 for previous residential assessment). Residential handlers are anticipated to have short-term dermal and inhalation exposures. The ARI approach was also used to assess residential handler risks as HIARC selected the same toxicological endpoints but different target MOEs for residential dermal and inhalation exposures. The combined ARI (for dermal and inhalation exposures) for homeowners performing broadcast treatments for lawn renovation via hand-held sprayer is 0.32, which exceeds HED's level of concern (HED's level of concern is for ARIs <1). The ARIs for homeowners performing spot treatments via low-pressure handwand and hose-end sprayer are 1.4 and 5.7, respectively, and do not exceed HED's level of concern.

In accordance with the HED Exposure Science Advisory Committee (ExpoSAC) guidance, the registered spot treatment use is not expected to result in significant post-application exposures and no post-application exposure assessment was conducted for this use. However, the registered lawn renovation use is expected to result in post-application dermal exposures to adults and toddlers and incidental ingestion exposure for toddlers; only short-term exposures are anticipated (HED's level of concern is for residential dermal and incidental oral MOEs <300). Based on the physical properties of glufosinate ammonium, no significant post-application inhalation exposures are anticipated. MOEs for dermal exposures by adults and toddlers are 40 and 24, respectively, and exceed HED's level of concern. Post-application incidental ingestion exposures (hand-to-mouth, object-to-mouth, and soil ingestion exposures) ranged from 310 to 93,000 resulting in an aggregate incidental oral exposure MOE of 250, which exceeds HED's level of concern. Since the HIARC selected the same endpoints for short-term incidental oral and short-term dermal, an aggregate assessment was conducted for dermal and incidental oral exposures (highest potential residential exposure; HED's level of concern is for aggregate dermal and incidental oral MOEs <300). The aggregate residential dermal and incidental oral MOE for toddlers was 22, which exceeds HED's level of concern.

Therefore, the registered lawn renovation use resulted in short-term incidental oral exposure and/or short-term dermal exposure for adults and children greater than HED's level of concern. The registered residential use for spot application around ornamentals resulted in residential exposures less than HED's level of concern.

Dietary Exposure Estimates: Acute (females 13-50 years old only; no acute dietary endpoint was identified for the general US population including infants and children) and chronic dietary exposure assessments

were performed using Dietary Exposure Evaluation Model (DEEM™; ver 7.76) which incorporates consumption data from the USDA 1989-92 Continuing Surveys of Food Intake by Individuals (CSFII). The acute dietary assessment assumed tolerance level residues, DEEM™ default processing factors, and 100% crop treated for all registered and proposed commodities. The chronic dietary assessment assumed tolerance level residues, DEEM™ default processing factors, and 3-year weighted average percent crop treated information for apple, canola, corn, and grape commodities (100% crop treated assumed for the remaining crops). The acute and chronic dietary food exposure estimates were less than HED's level of concern for the general US population and all population subgroups (<100% PAD). The acute analysis resulted in an exposure estimate for females 13-50 years old of 31% the aPAD. The most highly exposed population subgroup for the chronic analysis was children 1-6 years old at 48% the cPAD.

Estimated Drinking Water Concentrations: The HED Metabolism Assessment Review Committee (MARC) concluded that the residues of concern in drinking water are glufosinate ammonium, HOE 061517, HOE 064619, and N-acetyl-glufosinate. Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of the residues of concern in surface and ground water were made using computer models. Surface (FIRST ver 1.0; tier 1) and ground (SCIGROW ver 2.1; tier 1) estimated environmental concentrations (EECs) were generated using the registered application rate for apples, grapes, and tree nuts (3 applications at 1.5 lbs ai/acre; highest registered/proposed application rate). Surface water EECs were also generated using the interim rice model and the proposed application scenario for transgenic rice. The resulting EECs for the combined residues of glufosinate ammonium, N-acetyl- glufosinate, HOE 061517, and HOE 064619 are as follows: acute and chronic ground water (SCIGROW) - 0.86 µg/l; acute surface water (FIRST) - 356 µg/l; chronic surface water (FIRST) - 56 µg/l; and acute and chronic surface water (interim rice model) - 1168 µg/l

Aggregate Risk Assessment: HED conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Based on the proposed/registered uses for glufosinate ammonium, acute, short-term, and chronic aggregate exposure assessments were calculated. Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, drinking water levels of comparison (DWLOCs) were calculated. The DWLOC is the theoretical upper limit of a chemical's concentration in drinking water that will result in aggregate exposures less than HED's level of concern.

The registered lawn renovation use resulted in short-term incidental oral exposure and/or short-term dermal exposure for adults and children greater than HED's level of concern. Therefore, short-term aggregate exposure to glufosinate ammonium will exceed HED's level of concern. If the petitioner decides to revoke the lawn renovation use, then the following discussion concerning aggregate exposure assessment is applicable (residential exposure only from registered spot treatment use).

The acute (420 µg/l), short-term (69 - 130 µg/l), and chronic (100 - 610 µg/l) DWLOCs were greater than the EECs generated using the FIRST and SCIGROW models indicating aggregate exposures less than HED's level of concern. However, the acute, short-term, and chronic DWLOCs were less than the EECs generated using the interim rice model indicating aggregate exposure greater than HED's level of concern. The EECs generated by the interim rice model represent the concentration of the residues of concern in rice paddy water on the day of application. The only environmental fate parameter considered in the interim rice model is soil:water partitioning (pesticide management practices, degradation, and dilution when the paddy water is released are not considered). HED concluded that the more appropriate

estimate of residues in drinking water originating from surface water sources were the EECs generated using the FIRST model. Only the FIRST and SCIGROW EECs were used in the aggregate risk assessments. As a result, HED concludes that acute, short-term, and chronic aggregate exposures to glufosinate ammonium, as a result of all registered and proposed uses, are below HED's level of concern.

Recommendations for Tolerances: Section 3 registrations were requested by Aventis (transgenic rice and transgenic and nontransgenic cotton) and IR-4 (bushberry). A separate recommendation is written for each.

Transgenic Rice and Transgenic and Nontransgenic Cotton: Provided the petitioner revokes the currently registered lawn renovation use and submits revised Sections B and F, the toxicology, residue chemistry, and occupational/residential databases are sufficient for conditional registration and establishment of the following permanent tolerances for the combined residues of glufosinate ammonium (butonoic acid, 2-amino-4-(hydroxymethylphosphinyl) -, monoammonium salt), 2-acetamido-4-methylphosphinico-butanoic acid, and 3-methylphosphinico-propionic acid (all expressed as 2-amino-4-(hydroxymethylphosphinyl) butanoic acid):

rice, grain	1.0 ppm
rice, straw	2.0 ppm
rice, hull	2.0 ppm
cotton, undelinted seed	4.0 ppm
cotton, gin byproducts	15 ppm
egg	0.15 ppm
poultry, meat byproducts	0.60 ppm
poultry, meat	0.15 ppm
poultry, fat	0.15 ppm
milk	0.15 ppm
meat byproducts (cattle, goat, hog, horse, sheep)	6.0 ppm
meat (cattle, goat, hog, horse, sheep)	0.15 ppm
fat (cattle, goat, hog, horse, sheep)	0.40 ppm

Bushberry: Provided Aventis revokes the currently registered lawn renovation use and the petitioner submits a revised Section F, the toxicology, residue chemistry, and occupational/residential databases are sufficient for conditional registration and establishment of the following permanent tolerances for the combined residues of glufosinate ammonium, 2-acetamido-4-methylphosphinico-butanoic acid, and 3-methylphosphinico-propionic acid (all expressed as 2-amino-4-(hydroxymethylphosphinyl) butanoic acid):

bushberry crop subgroup (13B)	0.15 ppm

Unconditional registration may be granted upon submission of the following data:

- Blueberry field trial study conducted in Region 12 (n=1; residue decline data should be included).
- Comparative measurements of glutamine synthetase activity (brain, kidney and liver) in young and adult animals.
- A Developmental Neurotoxicity Study (DNT) in rats (previously required by HIARC).
- Repeat of Acute Neurotoxicity Study in rats with glufosinate ammonium (only) with adequate dosing as per the guideline. This study should also include measurements of glutamine synthetase activity (brain, kidney and liver).
- A 28-day inhalation toxicity study in rats with glutamine synthetase activity measurements in brain, kidney, liver and lung).
- Additional data are required to confirm that liver and kidney changes, observed in the absence of histopathological changes, are adaptive response and not an adverse effect. It should include kidney and liver function assays in addition to glutamine synthetase activity measurements and required routine parameters.

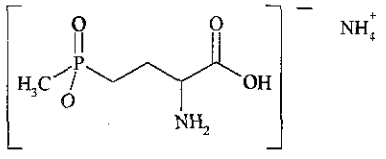
2.0 Physical Chemical Properties

The following information was obtained from a product chemistry review conducted by HED (PP# 8F3607, J. Garbus). Technical glufosinate ammonium is a racemic mixture of the D and L enantiomers.

2.1 Identification of Glufosinate Ammonium

CAS Chemical Name:	butonoic acid, (±)-2-amino-4- (hydroxymethylphosphinyl)-, monoammonium salt
IUPAC Chemical Name:	ammonium-DL-homoalanin-4-yl (methyl phosphinate)
Common Name:	glufosinate ammonium
Chemical Family:	organophosphorus
Chemical Type:	non-selective herbicide
PC Code Number:	128850
CAS Registry No.:	77182-82-2
Empirical Formula:	$C_5H_{15}N_2O_4P$
Molecular Weight:	198.19

2.2 Structure



glufosinate ammonium

2.3 Physical and Chemical Properties

Physical State:	crystalline powder
Vapor Pressure:	not determined
Partition Coefficient (n-Octanol/Water):	<0.1
Water Solubility:	1370 g/liter
Melting Point:	215 C
Density:	1.4 g/ml at 20 C

3.0 Hazard Characterization

The existing toxicity database for glufosinate ammonium is adequate for a conditional registration for application of glufosinate ammonium to a food/feed commodity. Unconditional registration may be granted upon submission of toxicity data addressing the deficiencies identified in Section 8.1. Tables 1 and 2 summarize the acute toxicity for glufosinate ammonium and the toxicity profile for glufosinate ammonium and its metabolites, respectively.

3.1 Hazard Profile

Glufosinate ammonium is toxicity category III for acute oral, dermal, and inhalation toxicities. It is toxicity category II for eye irritation. It is neither a dermal irritant nor a dermal sensitizer. For subchronic toxicity, the primary effects in the mouse were increased liver and kidney weights with increases in serum aspartate amino transferase and alkaline phosphatase. Signs of neurotoxicity were observed in rats in subchronic studies, such as aggressive behavior, piloerection, high startle response, increased incidence of fearfulness.

In the chronic studies in the rat, increased mortality, increased occurrence of retinal atrophy, and inhibition of brain glutamine synthetase were observed, as were increased liver and kidney weights. In the mouse, increased mortality was observed, as were changes in glucose levels consistent with changes in glutathione levels. Increased mortality and EKG alterations were observed in dogs. There was no evidence of a treatment-related increase in tumors.

The developmental toxicity study in the rat produced dilated renal pelvis and/or hydroureter in the offspring at levels that produced significant increases in hyperactivity and vaginal bleeding in dams. Therefore, there was no qualitative or quantitative evidence of increased susceptibility following *in utero* exposure in the prenatal developmental study in rats. There was evidence of qualitative increased susceptibility in the rabbit developmental study. Decreased fetal body weight and increased mortality observed at 20 mg/kg/day is considered more severe than the effects seen in rabbit dams which included decreased food consumption, body weight, and body weight gain were observed at 20 mg/kg/day.

The reproductive toxicity study in rats indicated postnatal developmental toxicity at the highest dose tested (HDT) in the form of decrease in viable pups. No parental toxicity was seen at the HDT. Since developmental effects were observed in the absence of parental toxicity, there is evidence of quantitative increased susceptibility in offspring.

A consistent pattern of neurotoxicity was seen in several studies, including the subchronic, developmental, and chronic studies in rats, mice, and dogs. In addition to the clinical signs such as hyperactivity, aggressive behavior, tono-clonic convulsion, piloerection, and high startle response, retinal atrophy was also observed. Changes in glutamine synthetase levels were observed in liver, kidney, and brain in rats. The HED HIARC concluded that the changes in liver and kidney glutamine synthetase activity and changes in liver and kidney weights were an adaptive response and not an adverse effect. The HIARC also concluded that the changes in brain glutamine synthetase activity are of significant concern. It is expected that the requested special studies will provide the information needed to confirm these conclusions and allow further characterize of these effects.

There is no concern for mutagenic activity in several studies including: Salmonella E. Coli, *in vitro*

mammalian cell gene mutation assays, mammalian cell chromosome aberration assays, *in vivo* mouse bone marrow micronucleus assays, and unscheduled DNA synthesis assays.

A rat metabolism study with dermal application indicated that about 50% of the administered radioactivity was absorbed 48 hours after a single dose application. In other metabolism studies, it was shown that over 80% of administered radioactivity is excreted within 24 to 48 hours as the parent compound in the feces and kidneys. In the urine, two metabolites (HOE 061517 and HOE 086486) were identified in minor amounts. In the feces, two additional metabolites (HOE 099730 and HOE 042231) were detected in minor amounts. Highest tissue levels were found in liver, kidney, and gonads.

Additional testing was conducted with HOE 061517 and HOE 099730 (metabolites of glufosinate ammonium) as well as with the L-isomer of glufosinate ammonium (HOE 058192). These compounds, tested in subchronic rat, mouse, and dog studies, and in developmental toxicity studies in rat and rabbit, showed a similar toxicity profile as the parent compound (HOE 039866).

Table 1: Acute Toxicity of Glufosinate ammonium Technical

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00142430, 00142431, 00142432	LD_{50} = 4010 mg/kg in males LD_{50} = 3030 mg/kg in females	III
81-2	Acute Dermal	00142436, 00142437	LD_{50} = >2000 mg/kg in males & females	III
81-3	Acute Inhalation	00151496, 00151497	LC_{50} = 4.42 m/L estimated in males & females	III
81-4	Primary Eye Irritation	00142438	eye irritant, corneal opacity reversible within 72 hours	III
81-5	Primary Skin Irritation	00142438	not a dermal irritant	IV
81-6	Dermal Sensitization	00142439	not a dermal sensitizer	N/A

Table 2: Toxicity Profile of Glufosinate Ammonium Technical

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents-rat (range-finding study)	45179103 (2000) Acceptable/nonguideline 0, 100 or 1000 ppm, Glufosinate 0, 6.2-8.8, or 64-90 mg/kg/day (males only) 0, 1000 or 10,000 ppm, N.acetyl-L-glufosinate 0, 65-90, or 657-935 mg/kg/day (males only)	Glufosinate ammonium NOAEL = 6.2-8.8 mg/kg/day in males LOAEL = 64-90 mg/kg/day in males, based on glutamine synthetase inhibition in the brains N-acetyl-L-glufosinate disodium NOAEL = 65-90 mg/kg/day in males LOAEL = 657-935 mg/kg/day in males, based on glutamine synthetase inhibition in the brains
870.3100 90-Day oral toxicity rodents-mouse	40345609 (1986) Acceptable/guideline 0, 80, 320 or 1,280 ppm; 0, 12, 48 or 192 mg/kg/day	NOAEL = 48 mg/kg/day in males, 192 mg/kg/day in females (HDT) LOAEL = 192 mg/kg/day in males, not achieved in females; based on the changes in clinical biochemistry and liver weights in males

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3200 Repeated Dose Dermal Toxicity-rat	40345605 (1985) Acceptable/guideline 0, 100, 300 or 1000 mg/kg/day	NOAEL= 100 mg/kg/day LOAEL= 300 mg/kg/day based on clinical observations (aggressive behavior, piloerection, and a high startle response)
870.3700a Prenatal developmental in rodents- rat	00142445, 00142446 (1982) 0, 0.50, 2.24 or 10 mg/kg/day	Maternal: NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on vaginal bleeding and hyperactivity Developmental: NOAEL = 50 mg/kg/day LOAEL =250 mg/kg/day based on dilated renal pelvis
	00151499, 00151500 (1982) 0, 0.50, 2.24 or 10 mg/kg/day 0, 10, 50 or 250 mg/kg/day	
	40345610 (1986) 0, 0.5, 2.24 or 10.0 mg/kg/day All three studies combined Acceptable/guideline	
870.3700b Prenatal developmental in nonrodents- rabbit	40345611, 41144703 (1984) Acceptable/guideline 0, 2.0, 6.3 or 20.0 mg/kg/day	Maternal: NOAEL = 6.3 mg/kg/day LOAEL = 20.0 mg/kg/day based on reduced food consumption, body weight and weight gains Developmental: NOAEL = 6.3 mg/kg/day LOAEL = 20.0 based on decreased body weights and fetal death
870.3800 Reproduction and fertility effects- rat	40345612 (1988) Acceptable/guideline 0, 40, 120 or 360 ppm 0, 2.0, 6.0, or 18.0 mg/kg/day	Parental/Systemic NOAEL = 18.0 mg/kg/day (HDT). LOAEL = not established Reproductive NOAEL = 6.0 mg/kg/day LOAEL = 18.0 mg/kg/day based on decreased number of viable pups Offspring NOAEL = 6.0 mg/kg/day LOAEL = 18.0 mg/kg/day based on decreased number of viable pups
870.4100b Chronic toxicity- dog	40345608 (1984) Acceptable/guideline 0, 2.0, 5.0 or 8.5 mg/kg/day	NOAEL = 5.0 mg/kg/day LOAEL = 8.5 mg/kg/day based on mortality (week 2) and alterations in the electrocardiogram at 6 months
870.4200 Carcinogenicity- rat	44539501 (1989) Acceptable/guideline 0, 1000, 5000 or 10000 ppm 0/0, 45.4/57.1, 228.9/281.5, or 466.3/579.3 mg/kg/day, M/F	NOAEL = 45.4 mg/kg/day in males, 57.1 mg/kg/day in females LOAEL = 228.9 mg/kg/day in males and 281.5 based on increased incidences of retinal atrophy no evidence of carcinogenicity
870.4300 Chronic/ Carcinogenicity- rat	40345607, 41144701 (1986) Acceptable/guideline 0, 40, 140 or 500 ppm 0/0, 1.9/2.4, 6.8/8.2, or 24.4/28.7 mg/kg/day, M/F	NOAEL = 24.4 mg/kg/day in males, 8.2 mg/kg/day in females LOAEL = not achieved in males and 28.7 based on inhibition of brain glutamate synthetase in females at 130 weeks no evidence of carcinogenicity
870.4300 Carcinogenicity- mice	40345609, 41144702 (1986) Acceptable/guideline 0, 20, 80, 160 (males only) or 320 (females only) ppm 0/0, 2.83/4.23, 10.82/16.19 or 22.60/66.96 mg/kg/day, M/F	NOAEL = 10.82 mg/kg/day in males, 16.19 mg/kg/day in females LOAEL = 22.60 mg/kg/day in males, 63.96 mg/kg/day in females based on increased mortality and glucose levels and consistent changes in glutathione levels in males, increased glucose levels and decreased albumin and total proteins no evidence of carcinogenicity at doses tested

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5265 Reverse Mutation Assay	Accession No. 072962 (1984) Acceptable/guideline 0, 5, 10, 50, 100, 500, and 1000 µg/plate	In a bacterial cell gene reverse mutation assay Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to glufosinate ammonium (92.1% a.i.) at concentrations of 0, 5, 10, 50, 100, 500, and 1000 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix). No increases in mutation frequencies, with or without metabolic activation, were noted in any of the test strains at any of the doses tested. Virtually total inhibition of growth was noted in all strains at the highest dose, 1000 µg/plate. Therefore, the requirement that chemicals be tested to the limits of cytotoxicity was satisfied. The positive controls, 2-aminoanthracene, AF-2, 1-ethyl-2-nitro-3-nitroso-guanidine, 9-amino-acridine, and 2-nitro-fluorine, induced the appropriate responses. Therefore the test systems were sensitive to agents that induce gene mutation. Under the conditions of the test, glufosinate- ammonium failed to cause reverse mutations in bacteria with and without metabolic activation.
870.5300 Detection of gene mutations in somatic cells in culture	40445616 (1988) Acceptable/guideline 50 to 5000 µg/mL 300 to 5000 µg/mL (S9-activated doses).	In a mouse lymphoma L5179Y forward mutation assay, HOE 039866 was tested at seven nonactivated doses of 50 to 5000 µg/mL or at six S9-activated doses of 300 to 5000 µg/mL. HOE 39866 did not increase the mutation frequency at the thymidine kinase locus. The solvent controls gave acceptable values and the positive controls ethylmethanesulfonate (nonactivated) and 3-methylcholanthrene (S9-activated) provided evidence that the assay had adequate sensitivity for detecting mutagenicity.
870.5395 In vivo mammalian cytogenetic tests	41144704 (1986) Acceptable/guideline 100, 200, and 350 mg/kg by gavage	In a mouse micronucleus assay 13 groups of mice (5/sex/dose) received a single administration of HOE 039866 at dose levels of 100, 200, and 350 mg/kg by gavage. A positive control group received 50 mg/kg of cyclophosphamide. After dosing, the animals were sacrificed at 24, 48, and 72 hrs., and the erythrocytes from the bone marrows were sampled at these times. The results indicated the test agent had no effect on micronucleus formation.
870.5500 Bacterial DNA damage or repair test	Accession No. 072962 (1984) Acceptable/guideline 0, 50, 100, 500, 1000, 5000 or 10,000 µg/plate.	In a DNA damage/repair assay, glufosinate ammonium was exposed overnight to B. subtilis that lacks the capacity for repair (H45) at concentrations of 0, 50, 100, 500, 1000, 5000 or 10,000 µg/plate. Glufosinate ammonium was also exposed, at the same dose levels, to an isogenic sister strain which has the capacity for DNA repair (H17). Under the conditions of the study, no difference in the inhibition of growth between these two strains was noted at any of the doses tested. Since the test measures the inhibition of growth in response to the test article, the requirement that chemicals be tested to the limits of cytotoxicity was satisfied. The positive controls, 2-(2-furyl)-3-(5-nitro-2-furyl)acrlamide (AF-2), caused a differential growth inhibition, whereas the negative controls (NaOH, HCL, and Kanamycin) produced no significant difference in growth inhibition. The test system was therefore sensitive to agents that damage DNA. **Under the conditions of the test, the test article failed to cause damage to DNA that could be detected by this repair assay.**

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5550 Unschedule DNA synthesis in mammalian cells in culture	40345614 (1984) Acceptable/guideline 0.1 to 5240 µg/mL	In an unscheduled DNA synthesis assay (MRID 40345614), primary rat hepatocyte cultures were exposed to HOE 039886 in deionized water at 15 concentrations ranging from 0.1 to 5240 µg/mL for 18 - 19 hours. HOE 039866 was tested up to cytotoxic concentrations as evidenced by decreased survival rate as low as 34% **There was no evidence that unscheduled DNA synthesis was induced by the test material.**
870.6200 Acute Neurotoxicity -rat	45190704 (1999) Acceptable/nonguideline 0, 10, 100 or 500 mg/kg	NOAEL= 500 mg/kg in males and females (HDT) LOAEL= Not established in both sexes
870.6200 Acute Neurotoxicity -rat	45190703 (1999) Acceptable/nonguideline 0, 10, 100 or 500 mg/kg	NOAEL= 500 mg/kg in males and females (HDT) LOAEL= Not established in both sexes
870.6200b Repeat Dose Neurotoxicity-rat	45179101, 45179102, 45297001 (2000) Acceptable/nonguideline 0, 20, 200 or 2000 ppm 0/0, 1.5/1.8, 14.9/17.1 or 143.3/161.5 mg/kg/day, M/F	NOAEL= 1.5 mg/kg/day in males, 1.8 mg/kg/day in females LOAEL= 14.9 mg/kg/day in males, 17.1 mg/kg/day in females, based on the inhibition of glutamate synthetase in the brain
870.6200b Repeat Dose Neurotoxicity-rat	42768201 (1993) Unacceptable/guideline 0, 7500, 10000 or 20000 ppm 0/0, 521.45/573.79, 685.95/740.57 or 1351.09/1442.64 mg/kg/day, M/F	NOAEL= Not established LOAEL= 521.45 mg/kg/day in males, 573.79 mg/kg/day in females based on increases in the incidence of decreased exploratory activity, decreased alertness, decreased startle response and meiosis
870.7485 Metabolism and pharmacokinetics - rat	43766913 (1993) Acceptable/nonguideline 2.0 mg/kg single dose	In a metabolism study (85-1), groups of Wistar rats (5/sex) received a single dose (2 mg/kg) of ^{14}C-Hoe 039866 (glufosinate ammonium) by gavage. The majority of the radioactivity (95-98% of the dose) was eliminated during the first 24 hrs after dosing. The parent compound, Hoe 039866, accounted for most of the eliminated radioactivity in the urine and feces of both males (80% of the dose) and females (73% of the dose). The metabolite, Hoe 061517, was consistently found in both urine and feces of both sexes. Hoe 099730 (7-8% of the dose) and Hoe 042231 (≈3% of the dose) were found in the feces of both male and female rats and none in the urine.
870.7485 Metabolism and pharmacokinetics - rat	43766914, 43778402 (1995) Acceptable/nonguideline 500 mg/kg single dose	In a metabolism study, groups of Wistar rats (5/sex or 2/sex) received a single dose (500 mg/kg) of ^{14}C-Hoe 039866 (glufosinate ammonium) by gavage. Animals were sacrificed at various times (2, 6, 24, and 96 hrs) after dosing. The majority of the radioactivity was eliminated during the first 24 to 48 hrs after dosing. The parent compound, Hoe 039866, accounted for the majority of the radioactivity eliminated in the excreta of both males (≈80% of the dose) and females (88% of the dose). This finding is consistent with the results of a previous metabolism studies (MRID No. 40345638 and MRID No. 43766913). The metabolite, Hoe 061517, was consistently found in both urine (0.22-1.20% of the dose) and feces (0.44-1.36% of the dose) of both sexes. Hoe 099730 was found in feces (0.28-1.72% of the dose) of both male and female rats and barely above or at the level of the detection in the urine of both sexes (0.02-0.04% of the dose). Hoe 042231 was mainly found in the feces of both male and females (≈0.2-0.28% of the dose). Very little if any of administered Hoe 039866 was sequestered in any tissues examined.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics - rat	40345640 (1985) Acceptable/nonguideline 30 mg/kg single dose	Groups of Wistar rats (5/sex) were orally administered a single nominal dose (30 mg/kg) of ^{14}C-HOE 039866. Rapid elimination during the first 24 hr for both males and females was observed. The major route of excretion was via feces (88% and 84% of the administered radioactivity for males and females, respectively). Within seven days of post dosing, greater than 94% of the dose was eliminated. Kinetics analysis indicated that the process of excretion was a two-phase process. The tissue radioactivity level for kidneys, liver and gonads was just above the background level.
870.7485 Metabolism and pharmacokinetics - rat	43766913 (1993) Acceptable/nonguideline 2.0 mg/kg single dose	In a metabolism study (85-1), groups of Wistar rats (5/sex) received a single dose (2 mg/kg) of ^{14}C-Hoe 039866 (glufosinate ammonium) by gavage. The majority of the radioactivity (95-98% of the dose) was eliminated during the first 24 hrs after dosing. The parent compound, Hoe 039866, accounted for most of the eliminated radioactivity in the urine and feces of both males (80% of the dose) and females (73% of the dose). The metabolite, Hoe 061517, was consistently found in both urine and feces of both sexes. Hoe 099730 (7-8% of the dose) and Hoe 042231 (≈3% of the dose) were found in the feces of both male and female rats and none in the urine.
870.7485 Metabolism and pharmacokinetics - rat	40345642 (1985) Acceptable/nonguideline 2.0 mg/kg/day (repeat dose 14 days)	Groups of Wistar rats (6/sex) were orally administered (gavage) unlabeled HOE 039866 for 14 days and ^{14}C-HOE039866 at the 15th day at a nominal dose of 2 mg/kg. The majority of the radioactivity was excreted within 24 hr after the last dose. The major route of elimination was via feces. There was also a two-phased elimination process. More radioactivity was found in the tissues of animals dosed repeatedly than that of animals receiving a single dose.
870.7600 Dermal Penetration-rat	40345620 (1986) Acceptable/guideline 0, 0.1, 1.0 or 10.0 mg/6cm^2	The results indicate that at the low dose (0.1 mg) 42.5 to 50.8% of the applied radioactivity was absorbed whereas at the high dose (10 mg) 26% was absorbed. After removal and washing of the treated skin a substantial amount of the radioactivity still remained in the skin, and it was gradually absorbed and eliminated. Radioactivity was found in both feces and urine samples, but the majority of HOE 039866 was eliminated in the urine. In all organs/tissues examined, radioactivity was found to reach a maximum level either at four or 10 hr after exposure. Subsequently, the radioactivity dropped rapidly. The amount of radioactivity found in the brain was very minimal relative to that of kidneys and liver.
HOE 061517 Metabolite		
870.3100 90-Day oral toxicity rodents-rat	44076206 (1988) Acceptable/guideline) 0, 400, 1600 or 6400 ppm 0/0, 30/32, 102/113 or 420/439 mg/kg/day M/F	NOAEL = 102 mg/kg/day in males, 113 mg/kg/day in females LOAEL = 420 mg/kg/day in males, 439 mg/kg/day in females based on increased in reticulocytes and increased in absolute and relative liver weights in males
870.3100 90-Day oral toxicity rodents-mice	44076207 (1989) Acceptable/guideline) 0, 320, 1600, 3200 or 8000 ppm 0/0, 46/47, 209/220, 496/561 or 1121/1340 mg/kg/day M/F	NOAEL = 1121 mg/kg/day in males, 1340 mg/kg/day in females LOAEL = Not established

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a Prenatal developmental in rodents- rat	44076209 (1994) Acceptable/nonguideline 0, 100, 300 or 900 mg/kg/day	Maternal: NOAEL = 300 mg/kg/day LOAEL = 900 mg/kg/day based on one death and clinical findings (persistent piloerection and/or increased urinary output) Developmental: NOAEL = 300 mg/kg/day LOAEL =900 mg/kg/day based on increases in the incidences of total litter loss and in the fetal and litter incidences of wavy and/or thickened ribs
870.3700b Prenatal developmental in nonrodents- rabbit	44076210 (1994) Unacceptable/guideline 0, 50, 100 or 200 mg/kg/day	Maternal: NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on increased abortions, mortality, and reductions in food and water consumption, body weight gain, and fecal output Developmental: NOAEL = 200 mg/kg/day LOAEL = Not observed
HOE 099730 metabolite		
870.3100 90-Day oral toxicity rodents-rat	44076201 (1994) Acceptable/guideline 0, 400, 2000 or 10,000 ppm 0/0, 29/32, 147/162 or 738/800 mg/kg/day M/F	NOAEL = 147 mg/kg/day in males, 162 mg/kg/day in females LOAEL = 738 mg/kg/day in males, 800 mg/kg/day in females based on glutamine synthetase inhibition in the brain
870.3100 90-Day oral toxicity rodents-mice	44076202 (1994) Acceptable/guideline 0, 500, 2000 or 8000 ppm 0/0, 83/110, 324/436 or 1296/1743 mg/kg/day M/F	NOAEL = Not established for males, 110 mg/kg/day in females LOAEL = 83 mg/kg/day in males, 436 mg/kg/day in females based on glutamine synthetase inhibition in the brain
870.3150 Subchronic Nonrodent Oral Toxicity-dog	44076203 (1994) Acceptable/guideline 0, 500, 2000 or 8000 ppm 0/, 19/21, 72/79 or 289/300 mg/kg/day M/F	NOAEL = 19 mg/kg/day in males, 21 mg/kg/day in females LOAEL = 72 mg/kg/day in males, 79 mg/kg/day in females based on glutamine synthetase inhibition in the brain
870.3700a Prenatal developmental in rodents- rat	44076204 (1993) Acceptable/guideline 0 or 1000 mg/kg/day	Maternal: NOAEL = 1000 mg/kg/day LOAEL = Not observed Developmental: NOAEL = 1000 mg/kg/day LOAEL = Not observed
870.3700b Prenatal developmental in nonrodents- rabbit	44076205 (1995) Acceptable/guideline 0, 64, 160 or 400 mg/kg/day	Maternal: NOAEL = 64 mg/kg/day LOAEL = 160 mg/kg/day based on reduced feed consumption Developmental: NOAEL = 64 mg/kg/day LOAEL = 160 based on uni- or bilateral extra at the 13th thoracic vertebra
870.6200 Acute Neurotoxicity -rat	45190702 (1999) Acceptable/nonguideline 0, 100, 1000 or 2000 mg/kg	NOAEL= 1000 mg/kg in males and females LOAEL= 2000 mg/kg in males and females based on clinical signs of toxicity including sedation, ruffled fur, and diarrhea
870.6200 Acute Neurotoxicity -rat	45190701 (1999) Acceptable/nonguideline 0, 100, 1000 or 2000 mg/kg	NOAEL= 100 mg/kg in males and females LOAEL= 1000 mg/kg in males and females based on decreased body weight gain

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200b Repeat Dose Neurotoxicity-rat	45179101, 45179102, 45297001 (2000); Acceptable/nonguideline 0, 20, 200 or 2000 ppm 0/0, 1.6/1.75, 15.5/17.7 or 158.9/179.4 mg/kg/day, M/F	NOAEL= 158.9 mg/kg/day in males, 179.4 mg/kg/day in females LOAEL= Not established in males and females
HOE 058192 Isomer		
870.3100 90-Day oral toxicity rodents-rat	44068501 (1989) Acceptable/guideline 0, 25, 250, 1250 or 2500 ppm 0/0, 1.9/1.9, 18.5/19.8, 91.8/100.3 or 186.4/194.3 mg/kg/day M/F	NOAEL = 18.5 mg/kg/day in males, 19.8 mg/kg/day in females LOAEL = 91.8 mg/kg/day in males, 100.3 mg/kg/day in females based on increased ammonia levels in the plasma and urine and slight kidney weight increases
870.3150 Subchronic Nonrodent Oral Toxicity-dog	44068502 (1989) Acceptable/guideline 0, 2, 5 or 8.5 mg/kg/day	NOAEL = 2 mg/kg/day LOAEL = 5 mg/kg/day based on increased plasma and kidney ammonia levels
870.3700b Prenatal developmental in nonrodents- rabbit	43829405 (1992) Acceptable/guideline 0, 1.25, 2.50, or 5.00 mg/kg/day	Maternal: NOAEL = 1.25 mg/kg/day ; LOAEL = 2.50 mg/kg/day based on decrease in body weight gains and food consumption, neurotoxic signs and abortions Developmental: NOAEL = 1.25 mg/kg/day; LOAEL = 2.50 mg/kg/day based on an increase in postimplantation loss (fetal resorptions)

3.2 FQPA Considerations

The HIARC determined that a 3x database uncertainty factor, due to the lack of a study that measures glutamine synthetase activity in the young and adult animals, should be applied to all dietary and residential dermal, inhalation, and incidental oral exposure assessments. The HIARC also determined that for residential inhalation exposure assessments an additional 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. For occupational, HIARC determined that a 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. The FQPA SFC determined that reliable data demonstrate that the safety of infants and children will be protected by use of the 3x (residential dermal, incidental oral, and dietary) and 30x (residential inhalation) database uncertainty factors set by HIARC; therefore, the special FQPA SF should be reduced to 1x (TXR No. 0050964). The decision made by the FQPA SFC was based on the following (a summary of the FQPA safety factors can be found in Table 3):

- The HIARC identified the following data gaps: acute neurotoxicity study conducted in the rat which includes glutamine synthetase activity measurement in the liver, kidneys, and brain; a developmental neurotoxicity (DNT) study conducted in the rat which includes comparative glutamine synthetase activity measurement in the liver, kidneys, and brain of the pups and mothers. The HIARC also requested additional data to confirm that liver and kidney changes, observed in the absence of histopathological changes, are an adaptive response and not an adverse effect. Kidney and liver function assays should be performed in addition to glutamine synthetase activity measurements. HIARC applied an additional traditional database uncertainty factor of 3x for the lack of the DNT study with comparative glutamine synthetase activity measurements. This is consistent with past practice for chemicals requiring a DNT

and comparative cholinesterase measurements.

- HIARC concluded that there is no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure in the prenatal developmental study in rats. There is qualitative evidence of increased susceptibility in the prenatal developmental study in rabbits and quantitative evidence of increased susceptibility in the 2-generation reproduction study in rats.

- No Special FQPA safety factor is necessary because: 1) there is no evidence of increased susceptibility of rat fetuses following *in utero* exposure in the developmental study with glufosinate ammonium. 2) Although there is qualitative evidence of increased susceptibility in the prenatal developmental study in rabbits and quantitative evidence of increased susceptibility in the 2-generation reproduction study in rats, the HIARC did not identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of glufosinate ammonium. The RfDs established are protective of pre-pre/postnatal toxicity following acute and chronic exposures. 3) The dietary food exposure assessment includes anticipated residues calculated from field trial data and available percent crop treated information from Biological Economic Analysis Division (BEAD; 100% crop treated is assumed for the new uses) and 4). EFED has indicated that the dietary drinking water exposure is based on conservative modeling estimates and the residential standard operating procedures (SOPs) will be used to assess post-application exposure to children as well as incidental oral exposure of toddlers, so these assessments will not underestimate the exposure and risks posed by glufosinate ammonium.

Table 3: Summary of FQPA Safety Factors for Glufosinate Ammonium

	LOAEL to NOAEL (UF_L)	Subchronic to Chronic (UF_S)	Incomplete Database (UF_{DB})		Special FQPA Safety Factor (Hazard and Exposure)
Magnitude of Factor	1X	1X	**3X**	**10X**	1X
Rationale for the Factor	No LOAEL to NOAEL extrapolations performed	No subchronic to Chronic extrapolations performed	**For lack of developmental neurotoxicity study with comparative glutamine synthetase measures**	**For lack of an adequate inhalation study and high concern for exposure via the inhalation route**	No residual uncertainties regarding pre- or post-natal toxicity or completeness of the toxicity or exposure databases.
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	**Dietary and residential oral, dermal, and inhalation exposure assessments (All durations)**	**All inhalation exposure assessments (All durations)**	Not Applicable

[1] combined FQPA safety factor of 30x to be applied to residential inhalation exposure assessments
[2] the HIARC concluded that this 10x factor should also be applied to occupational inhalation exposure assessments

3.3 Dose-Response Assessment

Table 4 summarizes the decisions made by the HIARC and the FQPA SFC concerning the dietary, residential, and occupational endpoints used in the current assessment. The HIARC determined that a 3x database uncertainty factor, due to the lack of a study that measures glutamine synthetase activity in the young and adult animals, should be applied to all dietary and residential dermal, inhalation, and incidental oral exposure assessments. The HIARC also determined that for residential inhalation exposure assessments an additional 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. For occupational, HIARC determined that a 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. The FQPA SFC determined that reliable data demonstrate that the safety of infants and children will be protected by use of the 3x (residential dermal and incidental oral, and dietary) and 30x (residential inhalation) database uncertainty factors set by HIARC; therefore, the special FQPA SF should be reduced to 1x. Short-, intermediate-, and long-term oral, dermal, and inhalation exposures can be combined due to same toxicity endpoints. The following text and Table 4 are a summary of the endpoints identified and used in the current risk assessment.

Acute Dietary Endpoint: The rabbit developmental toxicity study was chosen to selected for established in the aRfD of 0.021 mg/kg for Female 13-50 only. The NOAEL of 6.3 mg/kg was based on reduced fetal body weights and increased fetal deaths seen at the LOAEL of 20.0 mg/kg. A 300-fold uncertainty factor (consisting of: 3x database uncertainty factor; 10x for interspecies extrapolation; 10x for intraspecies variation) was incorporated in the acute RfD. The FQPA SFC determined that a special FQPA safety factor of 1x is applicable for acute dietary risk assessment. Thus, the aPAD is 0.021 mg/kg/day. An acute RfD for the general population (including infants and children) was not established because an endpoint attributable to a single exposure was not available from the toxicity studies including developmental studies.

Chronic Dietary Endpoint: A weight-of-evidence approach was used from three studies ((1) Two-year chronic toxicity/carcinogenicity study in rats, (2) 13-Week oral feeding study in rats (range finding study), and (3) Chronic feeding study in dogs) in establishing the cRfD of 0.02 mg/kg/day. The NOAEL of 6.0 mg/kg/day was based upon brain glutamine synthetase inhibition and alterations in the electrocardiogram seen in the above mention studies. A 300-fold uncertainty factor (consisting of: 3x database uncertainty factor; 10x for interspecies extrapolation; 10x for intraspecies variation) was incorporated into the chronic RfD. The FQPA SFC determined that a special FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is 0.02 mg/kg/day.

Carcinogenicity: The HIARC classified glufosinate ammonium as "not likely to be carcinogenic to humans" by all relevant routes of exposure based on adequate studies in two animal species; therefore, a cancer risk assessment is not required.

Short-Term Incidental Oral Endpoint: A short-term incidental oral endpoint was selected from the rabbit developmental toxicity study. The maternal NOAEL of 6.3 mg/kg/day was based upon reduced food consumption, body weight, and body weight gain at the LOAEL of 20.0 mg/kg/day. This study and endpoint are appropriate for the route and duration of exposure. The level of concern is for MOEs <300.

Short-Term Dermal Endpoint: Since no dermal study was available, a short-term dermal endpoint was selected from the rabbit developmental toxicity study. The maternal and developmental NOAEL of 6.3

mg/kg/day was based upon reduced food consumption, body weight, weight gains, reduced fetal body weight, and increased fetal mortality seen at 20 mg/kg/day (LOAEL). The HIARC determined that the dermal NOAEL of 100 mg/kg/day in the 21-day dermal toxicity study in rats is not protective of the effects seen in the oral developmental toxicity study in rabbits (the dermal study did not measure glutamine synthetase activity and developmental effects were not evaluated). Therefore, the HIARC selected an oral study for short-term dermal risk assessment. Since a NOAEL was selected from developmental toxicity study, a 60 kg body weight should be used in the calculating the human equivalent dose. Based on a rat dermal penetration study, a dermal absorption factor of 50% should be applied. The level of concern for residential exposure is for MOEs <300 and for occupational exposures is for MOEs <100.

Short-term Inhalation Endpoint: A short-term inhalation endpoint was chosen from the rabbit developmental toxicity. An inhalation absorption factor of 100% should be applied. The maternal and developmental NOAEL of 6.3 mg/kg/day was based upon reduced food consumption, body weight, weight gains, reduced fetal body weight, and increased fetal mortality seen at 20 mg/kg/day (LOAEL).

The HIARC evaluated the suitability of the 28-day inhalation toxicity study in rats with glufosinate ammonium (MRID 40345606) for this risk assessment. In this study, groups of Wistar rats were exposed to 0, 8, 20, or 46 mg/m^3 of glufosinate ammonium for 28 days over a period of 40 days. The NOAEL in this study was 8 mg/m^3 (converted to 2.2 mg/kg/day) based on clinical signs (tono-clonic convulsions, staggering gait etc.), and a decrease in thromboplastin time seen at 20 and 46 mg/m^3 (converted to 5.5 and 12.6 mg/kg/day). The HIARC concluded that this study is unsuitable for risk assessment because the particle size is too large, therefore, it decreases the confidence in the study LOAEL/NOAEL. Additionally, the critical effect, brain glutamine synthetase activity, was not measured. Although this study can not be used for risk assessment, the study indicates a high concern for exposure via the inhalation route since it demonstrates a lower NOAEL than those established in the oral studies, indicating that animals are more sensitive to effects by the inhalation route of exposure. The inhalation NOAEL of approximately 2.2 mg/kg/day is about three times lower than the oral NOAELs (6 mg/kg/day) used for end points selected for risk assessments. The HIARC also determined that for residential inhalation exposure assessments an additional 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. For occupational, HIARC determined that a 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. The level of concern for residential exposure is for MOEs <3000 and for occupational exposures is for MOEs <1000.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the

science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, glufosinate ammonium may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

Table 4: Doses and Toxicological Endpoints for the Exposure Scenarios Relevant to the Current Risk Assessment

Exposure Scenario	Dose and Uncertainty factor (UF)	Special FQPA Safety Factor and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary - females 13-50 years of age	NOAEL = 6.3 mg/kg/day UF = 300 aRfD = 0.021 mg/kg/day	FQPA SF = 1x aPAD = 0.021 mg/kg/day	Developmental Toxicity Study in Rabbits; LOAEL = 20 mg/kg/day; reduced fetal body weight and increased fetal death
Acute Dietary - general population including infants and children	No endpoint attributable to a single exposure was identified for the general population, including infants and children.		
Chronic Dietary - all populations	NOAEL= 6.0 mg/kg/day UF = 300 cRfD = 0.02 mg/kg/day	FQPA SF = 1x cPAD = 0.02 mg/kg/day	"Weight-of-evidence" approach from several studies; NOAEL = 6.0 mg/kg/day; brain glutamine synthetase inhibition and alterations in the electrocardiogram.
Cancer	Classification: Not likely to be carcinogen		
Short-Term Incidental Oral (1 - 30 Days)	NOAEL= 6.3 mg/kg/day UF = 300	FQPA SF = 1x MOE = 300 (residential)	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day; reduced food consumption, body weight, and body weight gain.
Short-Term Dermal (1 - 30 days)	Oral NOAEL=6.3 mg/kg/day 50% dermal absorption factor	FQPA SF = 1x MOE = 300 (residential) MOE = 100 (occupational)	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day; reduced fetal body weights, increased fetal mortality, reduced food consumption, body weight, and body weight gain
Short-Term Inhalation (1 - 30 days)	Oral NOAEL=6.3 mg/kg/day 100% inhalation absorption factor	FQPA SF = 1x MOE = 3000 (residential) MOE = 1000 (occupational)	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day; reduced fetal body weights, increased fetal mortality, reduced food consumption, body weight, and body weight gain

4.0 Exposure Assessment

Glufosinate ammonium is currently registered for broadcast application to the undesired vegetation in apple, grape, banana, and tree nut orchards (≤4.5 lbs ai/acre/year; pre-harvest interval (PHI) = 7 - 14 days); as a potato harvest aid (0.375 lbs ai/acre/year; PHI = 9 days); and as a foliar spray to the transgenic varieties of field corn, soybeans, sugar beet, and canola (≤1.1 lbs ai/acre/season; PHI = 60 - 70 days). Glufosinate ammonium is also registered for residential uses as a spot treatment around ornamentals (0.03 lbs ai/1000 ft^2) and for lawn renovation uses (1.36 lbs ai/acre).

4.1 Summary of Proposed Uses

The petitioners have proposed application of Liberty® Herbicide (18.19% glufosinate ammonium; soluble concentrate; EPA Reg. No. 264-660) to cotton, transgenic cotton, and transgenic rice and Rely® Herbicide (11.33% glufosinate ammonium; soluble concentrate; EPA Reg. No. 264-652) to bushberries. The Liberty® label indicates a 120-day plant back interval (PBI) for all crops except wheat, barley, buckwheat, millet, oats, rye, sorghum, and triticale where a 70-day PBI is indicated. Both labels prohibit application through irrigation equipment. The Rely® label also prohibits aerial application. Table 5 is a summary of the proposed application scenarios for transgenic rice, cotton, transgenic cotton, and blueberry.

The Liberty® label should include the following statements: (1) rice paddy water may not be used for irrigation purposes, as a water source for livestock, or for raising crayfish and (2) following treatment of cotton, the field may only be rotated to a registered crop. **A revised Section B is requested.**

Table 5: Proposed Use Patterns for Glufosinate Ammonium

Use Sites	Rice[1]	Cotton (transgenic and non transgenic)	Bushberry
Formulation	Liberty®, EPA Reg. No. 264-660, 18.19% ai, 1.67 lb ai/gal		Rely®, EPA Reg. No. 264-652, 11.33% ai, 1.00 lb ai/gal
Application rate	0.44 lb ai/acre/application, no more than 0.89 lb ai/acre per growing season	0.52 lb ai/acre/application, no more than 1.57 lb ai/acre per growing season	1.5 lb ai/acre/application (broadcast) no more than 3 lb ai/acre per 12-month period; 0.0312 lb ai/gal mix for backpack sprayer
Application timing	1-leaf through mid-tillering stage	transgenic and nontransgenic - planting through early bloom stage	not indicated
Application methods and spray volume	aerial (10 gallons/acre) and ground (10 gallons/acre)	transgenic - aerial (10 gallons/acre) and ground (15 gallons/acre) nontransgenic - hooded sprayer (15 gallons/acre)	ground only, including groundboom (broadcast) and backpack (spot treatment); spray directed to undesired vegetation; 20 gallons/acre
RTI (retreatment interval)	10-14 days	14 days	retreat as necessary
PHI	70 days		14 days
REI (reentry interval)	12 hours		

rice grown for seed may be treated

4.2 Dietary Exposure/Risk Pathway

A complete review of the residue chemistry data submitted in conjunction with the current petition can be found in D271110 (T. Bloem, 20-June-2002).

Nature of the Residue - Plants

HED has previously reviewed metabolism studies conducted with nontransgenic (corn, soybean, apple, and lettuce; 8F3607, J. Garbus, 14-Oct-1988 & 8-Aug-1990) and transgenic (corn, soybean, sugar beet, canola, and rice; D227386, M. Rodriguez, 7-Mar-1996; D257629, T. Bloem, 9-Jul-1999; 45204405.der.wpd) crops. HOE 061517 was the only metabolite identified in the nontransgenic studies (2-40% total radioactive residue (TRR); only soybean leaf, corn stover, and apples were analyzed). The petitioner demonstrated that 40% of the TRR in nontransgenic corn stover was incorporated into protein, starch, cellulose, and lignin. Glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 were the major residues identified in the transgenic crops (40-98% of the TRR). Based on the metabolism and magnitude of the residue studies, the MARC concluded that the residues of concern in the crops studied, for tolerance expression and risk assessment purposes, are glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 (D282757, T. Bloem, 9-May-2002). HED concludes that the results from the currently available metabolism studies may be translated to bushberry, cotton, transgenic cotton, and transgenic rice.

Nature of the Residue - Livestock

HED has previously reviewed lactating goat and laying hen metabolism studies (8F3607, J. Garbus, 14-Oct-1988 & 8-Aug-1990; D211531, M. Rodriguez, 7-Mar-1996). TRRs in muscle and fat from both studies were <0.01 ppm and were not further analyzed. Kidney, liver, and milk from the goat study and egg and liver from the hen study were analyzed with 36-90% of the TRR identified as glufosinate ammonium and HOE 064619. N-acetyl-glufosinate was identified as a minor metabolite in both the goat and hen studies (≤5% TRR). Unidentified metabolites were ≤2% TRR. Based on the metabolism and feeding studies, the MARC determined that the residues of concern in livestock, for tolerance expression and risk assessment purposes, are glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 (D282757, T. Bloem, 9-May-2002).

Residue Analytical Methods - Plants

Two analytical methods have been validated by the Analytical Chemistry Branch (ACB) for enforcement of the currently established tolerances: **(1)** nontransgenic - method HRAV-5A was validated by ACB for the determination of glufosinate ammonium and HOE 061517 in/on apple, grape, almond, soybean seed, corn grain, and corn forage (PP # 8F3607, J. Garbus, 14-Sep-1989) and **(2)** transgenic - method BK/01/99 was validated by ACB for determination of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 in/on canola seed and sugar beet root (D258420, T. Bloem, 19-Aug-2000). Both methods involve extraction with water, anion exchange chromatography, derivatization with trimethylorthoacetate, silica gel column clean-up, and quantification via gas chromatography with flame photometric detection (residues expressed as glufosinate free acid equivalents). Method BK/01/99 includes a cation ion exchange column prior to derivatization which fractionates glufosinate ammonium and N-acetyl-glufosinate and allows for speciation of these compounds (both are derivitized to the same compound). This step can be eliminated if separation of these two compounds is unnecessary.

The MARC has subsequently determined that the residues of concern for the currently registered and proposed transgenic and nontransgenic crops are glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517. HED concludes that method HRAV-5A is sufficient for enforcement of tolerances for these residues in/on the registered/proposed nontransgenic crops for the following reasons (no additional validation data are required): **(1)** the analytical procedures for HRAV-5A and BK/01/99 are essentially identical; **(2)** adequate recovery data for N-acetyl-glufosinate using method BK/01/99 as been attained in/on canola (seed, oil, meal), sugar beet (tops, root, dried pulp, molasses, sugar), corn (grain, forage, fodder, meal, flour, starch, oil), soybeans (seed, hay, meal, hull, oil), rice (grain, straw, bran, hull, polished rice), and cotton (seed gin byproducts, oil, hull, meal); and **(3)** based on the currently available metabolism studies, residues of N-acetyl-glufosinate are unlikely in nontransgenic crops.

The analytical methods used in the transgenic cotton and transgenic rice magnitude of the residue and processing studies were similar to method BK/01/95. Since this method has been validated by ACB and adequate validation has been submitted in conjunction with the magnitude of the residue and processing studies, HED concludes that method BK/01/95 is sufficient for enforcement of the rice and cotton tolerances.

Residue Analytical Methods - Livestock

Method HRAV-12 (also known as BK/01/95) has been validated by ACB for determination of glufosinate ammonium and HOE 061517 in/on milk, egg, muscle, and liver (PP# 8F3607, J. Garbus, 26-Oct-1994). Briefly, the method involves extraction with water, protein precipitation with acetone, anion exchange chromatography, derivatization with trimethylorthoacetate, silica gel column clean-up, and quantification via gas chromatography with flame photometric detection (residues expressed as glufosinate free acid equivalents).

The MARC has subsequently determined that the tolerance expression for livestock commodities will be for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517. The petitioner submitted a feeding study in which residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 were monitored in livestock commodities using method BK/03/95 (method was adequately validated; D211531, M. Rodriguez, 7-Mar-1996). Other than including procedures for quantitation of N-acetyl-glufosinate, method BK/03/95 is identical to the current enforcement method. Since BK/03/95 has been validated for determination of N-acetyl-glufosinate in livestock commodities and the analytical procedure is identical to that of current livestock enforcement method, HED concludes that the current enforcement method is sufficient for enforcement of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 livestock tolerances (no additional validation data are necessary).

Multiresidue Method

Glufosinate ammonium, HOE 061517, and N-acetyl-glufosinate were not quantitatively recovered from any of the FDA Multiresidue Testing Protocols. This information has been forwarded to FDA (PP#8F3607, J. Garbus, 14-Aug-1988; PP#5F4578, M. Rodriguez, 10-Oct-1995).

Storage Stability Data

As part of the current petition, the petitioner has submitted storage stability data indicating that residues of glufosinate ammonium and HOE 061517 are stable for 593 days on frozen blueberries (45580201.der2.wpd). Previously submitted and reviewed frozen storage stability data indicate that glufosinate ammonium and HOE 061517 are stable for 730 days on frozen apples, corn grain, and soybeans (PP#8F3607, J. Garbus, 8-Aug-1990) and glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 are stable for 12 months on transgenic soybean seed, forage and hay; for 3 months on soybean oil and meal; for 6 months on transgenic corn grain, fodder and forage; and for 24 months on transgenic sugar beet tops and roots (D211531 and D219069, M. Rodriguez, 7-Mar-1996; D257629, T. Bloem, 9-Jul-1999). These data are sufficient to validate the storage intervals and conditions for all the field trail and processing samples collected as part of the current petition.

Water, Fish, and Irrigated Crops

In support of the rice Section 3 request, the petitioner submitted a study investigating the residue levels of glufosinate ammonium, HOE 061517, and HOE 064619 in/on crops irrigated with rice paddy water treated with glufosinate ammonium (45204404.der.wpd).

Field trial sites in Rosa, LA and Porterville, CA were planted with transgenic rice and glufosinate ammonium was applied twice at 0.45 lbs ai/acre (1x proposed single and seasonal rate). At both sites, five, eight, and sixteen days after the second application, paddy water was used to irrigate test plots planted with grain sorghum (irrigated 71-88 days after planting), radish (irrigated 9-38 days after planting), collard (Louisiana site only; irrigated 49-60 days after planting), and lettuce (California site only; irrigated 27-38 days after planting). Irrigated crop samples collected 14 days after the last irrigation and at maturity were found to contain residues of glufosinate ammonium and/or HOE 061517 at <0.008 - 0.024 ppm. The petitioner has not provided the storage temperature for the crop samples prior to analysis. These data are necessary to validate the crop residue data. Additionally, HED has determined that the residues of concern in drinking water are glufosinate ammonium, HOE 061517, HOE 064619, and N-acetyl-glufosinate. These residues should have been monitored in the irrigated crops.

Despite the missing data, HED can conclude that residues of glufosinate ammonium and HOE 061517 are possible in/on crops irrigated with rice water paddy water treated with glufosinate ammonium. Therefore, the petitioner should include a statement prohibiting the use of treated rice paddy water for irrigation purposes on the proposed label. **A revised Section B is requested.**

Meat, Milk, Poultry and Eggs

Ruminant: Based on the results of the ruminant feeding studies (PP#8F3607, J. Garbus, 8-Aug-1990 and D211531, M. Rodriguez, 7-Mar-1996) and the current MTDB for ruminants (beef cattle - 15.38 ppm; aspirated grain fractions, corn field forage, cannery waste, cotton gin byproducts), HED concludes that the following tolerances for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 are appropriate: meat (cattle, goat, hog, horse, sheep) - 0.15 ppm; meat byproducts (cattle, goat, hog, horse, sheep) - 6.0 ppm; fat (cattle, goat, hog, horse, sheep) - 0.40 ppm; and milk - 0.15 ppm. **A revised Section F is requested.**

Poultry: Based on the results of the poultry feeding studies (PP#8F3607, J. Garbus, 8-Aug-1990 and D211531, M. Rodriguez, 7-Mar-1996) and the current MTDB for poultry (3.33 ppm; soybean hulls, soybean meal, soybean seed, cotton meal), HED concludes that the following tolerances for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 are appropriate: poultry, meat - 0.15 ppm; poultry, meat byproducts - 0.60 ppm; poultry, fat - 0.15 ppm; and egg - 0.15 ppm. **A revised Section F is requested.**

Crop Field Trials

Bushberry: Glufosinate ammonium formulated as a soluble concentrate was applied twice as a spray directed to the soil at 1.50 lbs ai/acre (1x the maximum proposed single and seasonal application rates; RTI - 25-29 days). Blueberries were harvested at maturity 13-15 days after the final application. Combined residues of glufosinate ammonium and HOE 061517 ranged from <0.03 - 0.08 ppm (residues in/on controls were <0.02). The petitioner has not submitted residue decline data. HED has determined that the tolerance expression for bushberries will be for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517. Residues of N-acetyl-glufosinate were not monitored in the blueberry magnitude of the residue study. The method used in the blueberry field trials is identical to that used to monitor for residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 in the transgenic cotton and transgenic rice studies summarized below. These studies indicate that glufosinate ammonium and N-acetyl-glufosinate are derivatized to the same compound and quantified together. For this reason and since the metabolism studies indicated that residue of N-acetyl-glufosinate are unlikely in nontransgenic crops, HED is willing to conclude that the submitted blueberry field trial data has adequately accounted for residues of N-acetyl-glufosinate in/on blueberry.

Provided the petitioner agrees to conduct a blueberry field trial in Region 12 (n=1; residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 should be monitored; residue decline data should be included), HED concludes that the available field trial data is sufficient to support establishment of the following permanent tolerance for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517: bushberry crop subgroup (13b) 0.15 ppm. A revised section F is requested.

Transgenic Cotton: Liberty™ (water soluble liquid formulation; 18.2% glufosinate ammonium) was applied three times at ~0.50 lbs ai/acre with the first and third made using over the top broadcast spray equipment and the second application directed at the bottom third of the plant (1x the maximum proposed single and seasonal application rates; RTI = 7-28 days). Cotton was harvested by hand (n=6) or mechanically with spindle (n=4) or stripper (n=4) pickers 67-76 days after the last application. Combined residues of glufosinate ammonium/N-acetyl-glufosinate and HOE 061517 in/on cottonseed and cotton gin byproducts ranged from <0.10 - 3.33 ppm and 0.95 - 11.63 ppm, respectively (residue in/on controls <0.10 ppm; LOQ = 0.10 ppm). HED concludes that the available field trial data is sufficient to support establishment of the following permanent tolerances for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517: cotton, undelinted seed - 4.0 ppm and cotton, gin byproducts - 15 ppm. **A revised Section F is requested.**

Cotton: The petitioner is also requesting hooded spray application to nontransgenic cotton (seasonal total of 1.57 lbs ai/acre). Field trial data depicting only hooded spray applications have not been submitted.

Since hooded spray applications are likely to result in residues less than those demonstrated with over the top applications, residue data reflecting only directed applications are unnecessary.

Transgenic Rice: Liberty™ (water soluble liquid formulation; 18.2% glufosinate ammonium) was applied twice to transgenic rice at 0.45-0.50 lbs ai/acre (1x maximum proposed single and seasonal application rates; RTI of 12-29 days). Combined residues of glufosinate ammonium/N-acetyl-glufosinate and HOE 061517 in/on rice grain and rice straw ranged from <0.10 - 0.74 ppm and <0.10 - 1.48 ppm, respectively (residues in/on controls were <0.05). HED concludes that the available field trial data is sufficient to support establishment of the following permanent tolerances for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517: rice, grain 1.0 ppm and rice, straw - 2.0 ppm. **A revised Section F is requested.**

Processed Food/Feed

Cotton: Transgenic cotton was treated with Liberty™ herbicide (water soluble liquid; 18.2% glufosinate ammonium) at 2.7x the maximum proposed seasonal application rate. Cotton was mechanically harvested 76 days after the last application and processed into cottonseed, cottonseed meal, cottonseed hull, and cottonseed refined oil. The resulting residue analytical data indicate that the combined residues of glufosinate ammonium/N-acetyl-glufosinate and HOE 061517 reduced in cottonseed refined oil (0.01x) and concentrated in cottonseed hull (1.2x) and cottonseed meal (1.3x).

Based on the cottonseed highest average field trial (HAFT) of 3.24 ppm from the magnitude of the residue study (45089303.der.wpd); the recommended cottonseed tolerance of 4.0 ppm; and the meal (1.3x), hull (1.2x), and refined oil (0.01x) processing factors, HED concludes that tolerances for cottonseed processed commodities are unnecessary. Tolerances for cottonseed oil, cottonseed meal, and cottonseed hull will be covered by the unprocessed raw agricultural commodity (RAC).

Transgenic Rice: Transgenic rice was treated with Liberty™ herbicide (water soluble liquid; 18.2% glufosinate ammonium) at 5x the maximum proposed seasonal application rate. Rice grain was harvested at maturity 78 days after the last application and processed into rice hull, rice bran, and polished rice. The resulting analytical data indicate that the combined residues of glufosinate ammonium/N-acetyl-glufosinate and HOE 061517 reduced in rice bran (0.8x) and concentrated in rice hull (2.8x) and polished rice (1.3x).

Based on the rice grain HAFT of 0.74 ppm from the magnitude of the residue study (45204406.der.wpd) and the rice hull (2.8x) concentration factor, HED concludes that the following tolerances for the combined residues of glufosinate ammonium, N-acetyl-glufosinate, and HOE 061517 are appropriate: rice, hulls - 2.0 ppm. **A revised Section F is requested.** Tolerances for rice bran and polished rice will be covered by the unprocessed RAC.

Confined/Field Accumulation in Rotational Crops

A confined rotational crop study has been submitted and reviewed (D211531 and D219069, M. Rodriquez, 7-Mar-1996). Lettuce, radish, and spring wheat were planted 28 and 119 days after the soil was treated with [3,4-^{14}C]-HOE-039866 at 0.9 lbs ai/acre (0.6x and 1.0x the maximum proposed application rate for cotton and rice, respectively; bushberries are not rotated). All samples planted 28 days after treatment were analyzed. HOE 061517 (5-57% TRR) and HOE 064619 (6-10% TRR) were the only compounds identified (a total of 32-64% of the TRR was identified). Except for the wheat commodities, TRRs were

≤0.02 ppm for the samples planted 120 days after treatment (wheat commodities 0.06-0.15 ppm).

A wheat field rotational crop study has also been submitted and reviewed (P. Errico [RD], 6-May-1998). Wheat was planted 73 - 90 days after the soil was treated with glufosinate ammonium at 0.8 lbs ai/acre (0.5x and 0.9x the maximum proposed application rate for cotton and rice, respectively). Wheat forage, hay, straw, and grain were harvested at maturity and analyzed for residues of glufosinate ammonium and HOE 061517 (residues were <LOQ; LOQ = 0.05 ppm).

Based on the confined and field rotational crop studies, the MARC determined that the residues of concern in rotational crops, for tolerance expression and risk assessment purposes, are glufosinate ammonium, HOE 061517, and HOE 064619 (D282757, T. Bloem, 9-May-2002). The Liberty® label indicates a 120-day PBI for all crops except wheat, barley, buckwheat, millet, oats, rye, sorghum, and triticale where a 70-day PBI is indicated. Based on the results from the confined and field rotational studies, HED concludes that the proposed rotational crop restrictions are appropriate for rice. The currently available confined and field rotational crop studies were conducted at 0.5-0.6x the maximum proposed application rate for cotton. As a result, the magnitude of the residues in/on the rotated crops are not representative of that which would be attained following rotation to a cotton field treated with glufosinate ammonium. Therefore, the petitioner should amend the label indicating that within 12 months of the final glufosinate ammonium application, the treated field may only be rotated to a registered crop. **A revised Section B is requested.**

International Harmonization of Tolerances

Codex and Mexico do not have maximum residue limits (MRLs) for residues of glufosinate ammonium, N-acetyl-glufosinate, or HOE 061517 in/on the proposed crops or livestock commodities. Canada does not have MRLs for residues of glufosinate ammonium, N-acetyl-glufosinate, or HOE 061517 in/on the proposed crops, poultry commodities, or milk but does have a MRL of 1 ppm for ruminant liver and kidney. The meat byproduct tolerance determined to be appropriate by HED is greater than the Canadian MRL, therefore harmonization is not appropriate.

4.3 Dietary Exposure Analysis

Acute and chronic dietary exposure assessments were conducted using the DEEM™ software Version 7.76, which incorporates consumption data from USDA's CSFII, 1989-1992 (D283555, T. Bloem, 25-Jul-2002). The 1989-92 CSFII data are based on the reported consumption of more than 10,000 individuals over three consecutive days and, therefore, represent more than 30,000 unique "person days" of data. Foods "as consumed" (i.e., apple pie) are linked to RACs and their food forms (i.e., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In

accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified and noted in the risk assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (i.e., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys (i.e., nursing infants). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (*i.e.*, all infants or females 13-50 years old). Thus, the population subgroups listed in Table 5 include those subgroups having sufficient numbers of survey respondents in the 1989-1992 CSFII food consumption survey.

acute: The HIARC identified an acute endpoint for females 13-50 years old (acute endpoint was not identified for the general US population including infants and children). The acute dietary assessment assumed tolerance level residues, DEEM™ default processing factors, and 100% crop treated for all registered and proposed commodities. The resulting exposure estimate for females 13-50 years old was less than HED's level of concern (<100% PAD). Table 6 includes a summary of the acute dietary exposure analysis.

chronic: The chronic dietary assessment assumed tolerance level residues, DEEM™ default processing factors, and 3-year weighted average percent crop treated information for apple, canola, corn, and grape commodities (100% crop treated assumed for the remaining crops). The resulting exposure estimated were less than HED's level of concern for the general US population and all population subgroups (<100% PAD). The most highly exposed population subgroup for the chronic analyses was children 1-6 years old (48% cPAD). Table 6 includes a summary of the chronic dietary exposure analysis.

cancer: Glufosinate ammonium has been classified as "not likely to be a carcinogen." Therefore, a cancer analysis was not performed.

Table 6: Results of Acute and Chronic Dietary Exposure Analyses

Population Subgroup	Acute Dietary			Chronic Dietary		
	aPAD (mg/kg/day)	Dietary Exposure[1] (mg/kg/day)	%aPAD[1]	cPAD (mg/kg/day)	Dietary Exposure (mg/kg/day)	%cPAD
U.S. population - total	na	--	--	0.02	0.003894	20
All Infants (<1 year old)	na	--	--	0.02	0.009391	47
Children (1-6 years old)	na	--	--	0.02	0.009522	48
Children (7-12 years old)	na	--	--	0.02	0.006203	31
Females (13-50 years old)	0.021	0.006423	31	0.02	0.002756	14
Males (13-19 years old)	na	--	--	0.02	0.004301	22

Males (20+ years old)	na	--	--	0.02	0.002903	14
Seniors (55+ years old)	na	--	--	0.02	0.002589	13

na = not applicable
[1] 95th percentile

4.4 Water Exposure/Risk Pathway

The following information was provided by EFED (D280453, J. Ravenscroft, 30-July-2002). At the present time, there are no surface or ground water monitoring data available. Based on the environmental fate studies, the MARC concluded that glufosinate ammonium, HOE 061517, HOE 064619, and N-acetyl-glufosinate are residues of concern in drinking water for purposes of risk assessment.

Environmental Fate Assessment: Available environmental fate studies indicate glufosinate-ammonium is relatively stable and is very mobile (K_d = 1.5; K_{oc} = 173; water solubility 1370 g/l). It dissipated with a first order half-life ranging from 4.3 – 10.3 days on bare ground and 8 – 30 days on cropped fields following a single application. The main degradation pathway in water and soil is via microbial action, metabolizing primarily to CO_2, HOE 061517, 2-methylphosphinico acetic acid (HOE 064619), and 2-acetamido-4-methylphosphinico-butanoic acid. Aerobic soil metabolism produced a half-life of approximately 4 – 23 days; metabolite concentrations peaked at 3 weeks and then began to decline. Anaerobic soil metabolism produced a half-life of 56 days. The aerobic aquatic metabolism half-life was 64 days in gravel pit water sand sediment.

Glufosinate may leach to ground water under certain conditions (such as in areas of sandy soils with high permeability and shallow ground water). Degradates HOE 061517 (K_d = 0.7 and K_{oc} = 84) and N-acetyl-glufosinate (K_d = 0.8) are more mobile than the parent, and may also be expected to leach to ground water. However, the potential for degradate 064619 to leach to ground water is much lower because of its higher adsorption coefficient (K_d = 24).

Ground and Surface Water EECs: Surface (FIRST; ver 1.0; tier 1) and ground (SCIGROW; ver 2.1; tier 1) water EECs were generated for glufosinate ammonium, HOE 061517, HOE 064619, and N-acetyl-glufosinate based on the registered application rate for apples, grapes, and tree nuts (3 applications at 1.5 lbs ai/acre; highest registered/proposed rate). Surface water EECs for glufosinate ammonium and its degradates were also generated using the interim rice model and the proposed application scenario for transgenic rice. The only environmental fate parameter considered by the interim rice model is soil:water partitioning (pesticide management practices, degradation, and dilution when the paddy water is released are not considered). These models are all conservative screening level models. The resulting EECs for the combined residues of glufosinate ammonium, HOE 061517, HOE 064619, and N-acetyl-glufosinate are summarized below.

ground water EECs:	acute and chronic - 0.86 µg/l
FIRST surface water EECs:	acute - 356 µg/l; chronic - 56 µg/l
interim rice model surface water EECs:	acute and chronic - 1168 µg/l

4.4 Residential and non-Occupational Exposure/Risk Pathway

Glufosinate ammonium is registered for residential (outdoor, non-food) products as a non-selective, postemergent herbicide and is primarily used as a spot treatment around trees, shrubs, fences, walks, patios, driveways, sidewalks, and flower beds. It is also registered for lawn renovation uses (Finale® Super Concentrate, EPA Reg. No. 45639-191). Potential residential exposures for the use of glufosinate ammonium include:

- Homeowner application, both broadcast and spot treatment: short-term dermal and inhalation exposures.
- Post-application short-term incidental oral exposures by toddlers, including:
  - non-dietary, incidental oral hand-to-mouth.
  - non-dietary, incidental oral object-to-mouth (turf mouthing).
  - non-dietary, ingestion of treated soil.
- Post-application short-term dermal exposures by adults and toddlers.

Residential exposures were previously assessed by HED (D258145, M. Christian, 7-Sep-1999). The exposure and risk estimates presented below serve as an update to this assessment based on revisions to residential exposure assessment policies as summarized below:

- *For residential handler exposure assessment:* Summary of HED's Reviews of Outdoor Residential Exposure Task Force (ORETF) Chemical Handler Exposure Studies; MRID 449722-0. ORETF Study OMA004 (hose-end sprayer), April 30, 2001. Note that Aventis CropScience is a member of ORETF.
- *For residential post-application exposure assessment: Standard Operating Procedures (SOPs) For Residential Exposure Assessments*, Draft, 17-Dec-1997 and Science Advisory Committee for Exposure (ExpoSAC Policy) No. 11, 22-FEB-2001: *Recommended Revisions to the SOPs for Residential Exposure.*

Homeowner Handler/Applicator Exposure Assumptions and Risk Assessment: The updated residential exposure and risk assessment for homeowner handler/applicator is presented in Table 7. The short-term dermal and short-term inhalation exposure estimates were combined since the same toxicological endpoint was selected for each. Since the target MOEs for residential dermal (>300) and inhalation (>3000) exposures are different, an ARI approach was used to aggregate dermal and inhalation risks to residential handlers. HED's level of concern is for ARIs <1 (see HED's *Guidance for Performing Aggregate Exposure and Risk Assessments*, 29-OCT-1999).

Table 7: Updated Homeowner Handler Exposure and Risk Assessment for Registered Uses of Glufosinate Ammonium on Residential Lawns

Exposure Scenario	Unit Exposure[1] (mg/lb ai handled)	AR[2]	Size lawn/ garden treated/d[3]	PDR[4] (mg/kg/day)	Short-term Dermal MOE[5]	Short-term Inhalation MOE[5]	Short-term ARI[6]
Residential handler, broadcast treatment with hose-end sprayer	dermal, short pants, short sleeves: 11 (HC)	1.36 lb ai/acre for lawn renovation	0.5 acres	dermal: 0.0623	100	35,000	**0.32**
	inhalation: 0.016 (HC)			inhalation: 0.000181			
Residential handler, spot treatment with hose-end sprayer	dermal, short pants, short sleeves: 11 (HC)	0.0312 lb ai/1000 ft^2	1,000 ft^2	dermal: 0.00286	2,200	760,000	5.7
	inhalation: 0.016 (HC)			inhalation: 8.33×10^{-6}			
Residential handler, spot treatment with low-pressure handwand	dermal: 56	0.0312 lb ai/1000 ft^2	1,000 ft^2	dermal: 0.0146	430	1.9×10^6	1.4
	inhalation: 0.0065			inhalation: 3.39×10^{-6}			

[1] Source: Summary of HED's Reviews of ORETF Chemical Handler Exposure Studies; MRID 449722-0. ORETF Study Number OMA004 (hose-end sprayer), April 30, 2001; HC = high confidence data. Low-pressure handwand unit exposure data from ORETF residential study, MRID 44518501 (Merricks, 1998) conducted with liquid carbaryl on trees and ornamental plants. Note that this study has been preliminarily reviewed by HED, but confidence levels have not been assigned. However, HED considers this data to be acceptable for Tier 1 screening level assessments.

[2] AR = Maximum application rate; Source: Registered label, Finale Super Concentrate, EPA Reg. No. 45639-191.

[3] Daily acres treated Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.

[4] PDR = Unit exposure(mg/lb ai) x AR x Acres/Day x 1/BW (60 kg per HIARC since dermal and inhalation endpoints selected from developmental toxicity study) x %Absorption (50% dermal absorption and 100% inhalation absorption rate per HIARC).

[5] MOE = NOAEL/PDR; short-term dermal and inhalation NOAEL = 6.3 mg/kg bw/day.

[6] ARI = 1/(((1 ÷ (calculated dermal MOE ÷ target MOE)) + (1 ÷ (calculated inhalation MOE ÷ target MOE))).

Homeowner and Toddler Post-Application Exposure Assumptions and Risk Estimates: In accordance with ExpoSAC guidance, the registered spot treatment use is not expected to result in significant post-application exposures and no post-application exposure assessment was conducted for this use. However, the registered lawn renovation use is expected to result in post-application dermal exposures to adults and toddlers and incidental oral exposure for toddlers; only short-term exposures are anticipated. Based on the physical properties of glufosinate ammonium, no significant post-application inhalation exposures are anticipated. The post-application residential assessment assumed that a homeowner performed a lawn renovation treatment up to the maximum application rate of 1.36 lb ai/acre as specified on the Finale® Super Concentrate label (EPA Reg. No. 45639-191). The Finale® label indicates that weed kill activity is anticipated in 1 to 4 days. Since lawn renovation is typically a one-time event, only short-term exposures are anticipated, which is further supported by environmental fate data. In the terrestrial field dissipation study (MRID 431104-02), first-order half-lives ranged from about 4 to 10 days on bare ground and about 8 to 30 days on cropped fields following a single application. The following paragraphs summarize the assumptions used in the post-application assessment.

Dermal Exposures (Adults and Toddlers): The assumptions listed below were used to assess dermal exposures by adults and toddlers after contact with treated lawns. HED's level of concern is for residential dermal MOEs <300.

- Adult and toddler body weights are 70 kg and 15 kg, respectively.
- 5% of maximum application rate represents the fraction of glufosinate ammonium available as dislodgeable residue on the day of treatment.
- Dermal transfer coefficient for adults is 14,500 cm^2/hr and for toddlers, 5,200 cm^2/hr.
- Daily duration of exposure: 2 hours.

Table 9: Risk Assessment for Post-Application Dermal Exposure following Application of Glufosinate Ammonium for Lawn Renovation[1]

Exposure Scenario	AR (lbs a.e./A)[2]	DFR (µg/cm^2)[3]	PDR (mg/kg bw/d)[4]	Short-term Dermal MOE[5]
Adult	1.36	0.763	0.158	40
Toddler			0.265	24

[1] Sources: Standard Operating Procedures for Residential Exposure Assessments, Draft, December 17, 1997 and Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.

[2] AR = maximum application rate by LCO performing residential lawn treatment.

[3] DFR = 1.36 lb ai/acre x 0.05 x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) = 0.763 µg/cm^2

[4] PDR = (0.763 µg/cm^2 x 0.001 mg/µg x TC (cm^2/hr) x 2 hrs/d x 50% dermal absorption/BW (70 kg for adults and 15 kg for toddlers). Note: TC for adults, short-term = 14,500 cm^2/hr; TC for toddlers, short-term = 5,200 cm^2/hr.

[5] MOE = NOAEL/PDR, where the short-term dermal NOAEL = 6.3 mg/kg/day. HED's level of concern for dermal exposures is for MOEs <300 (residential).

The short-term MOEs for post-application dermal exposure for adults and toddlers, as a result of the registered lawn renovation use, are **40** and **24**, respectively, and exceed HED's level of concern. Note that this is Tier 1 screening level assessment based on exposure to residues on the day of treatment.

Hand-to-Mouth Exposure Assessment Assumptions (Toddlers): HED believes that incidental "ingestion" might occur on a repeated basis as a result of "normal" hand-to-mouth behavior, and thus, herbicide that has been applied to the turf, including residues on soil, may be ingested. Therefore, the toxicological endpoint used to evaluate incidental ingestion by toddlers are the incidental oral endpoints. HED's level of concern is for incidental oral MOEs <300. The following assumptions were used to assess exposures to toddlers after contact with treated lawns:

- toddler body weight: 15 kg.
- toddler hand surface area is 20 cm^2, and a toddler performs 20 hand-to-mouth events per hour for short-term exposures.
- exposure duration: 2 hours per day.
- 5% of application rate represents fraction of glufosinate ammonium available for transfer to hands on the day of treatment with a 50% saliva extraction factor for hand-to-mouth exposures.
- For object-to-mouth exposures, 20% of application rate available as dislodgeable residues on the day of treatment, and the "object" is approximately 25 cm^2.
- 100% of application rate is available in the top 1 cm of soil for soil ingestion exposures. Also, it is assumed that a toddler can ingest 100 mg soil/d.

Table 8: Risk Assessment for Post-Application Toddler Incidental Ingestion Exposure following Application of Glufosinate Ammonium for Lawn Renovation[1]

Activity	AR (lbs ai/acre)[2]	Residue Estimate[3]	PDR (mg/kg/day)[4]	Short-term MOE[5]
Hand-to-mouth	1.36	DFR: 0.763 µg/cm^2	0.0203	310
Object-to-mouth		DFR: 3.05 µg/cm^2	0.00508	1,200
Soil Ingestion		Soil residue: 10.2 µg/g soil	6.80×10^{-5}	93,000
Aggregate incidental ingestion exposure			0.0254	**250**

[1] Sources: Standard Operating Procedures for Residential Exposure Assessments, Draft, December 17, 1997 and Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.

[2] AR = maximum application rate on registered label, Finale® Super Concentrate, EPA Reg. No. 45639-191 under "Lawn Renovation."

[3] Residue estimates based on the following protocol from the Residential SOPs:
   a. Hand-to-mouth DFR = 1.36 lb ai/acre x 0.05 x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) = 0.763µg/cm^2.
   b. Object-to-mouth DFR = 1.36 lb ai/acre x 0.20 x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) = 3.05 µg/cm^2.
   c. Soil Res. = 1.36 lb ai/acre x fraction of residue in soil (100%)/cm x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) x 0.67 cm^3/g= 10.2 µg/g soil.

[4] Potential Dose Rate (PDR; normalized to body weight of toddler):
   a. Short-term Hand-to-mouth PDR = (0.763 µg/cm^2 x 0.50 x 20 cm^2/event x 20 events/hr x 10^{-3} mg/µg x 2 hrs/d)/15 kg = 0.0203 mg/kg bw/d
   b. Object-to-mouth PDR = (3.05 µg/cm^2 x 25 cm^2/d x 10^{-3} mg/µg)/15 kg = 0.00508 mg/kg bw/d.
   c. Soil Ingestion PDR = (10.2 µg/g soil x 100 mg soil/d x 10^{-6} g/µg)/15 kg = 6.80×10^{-5} mg/kg bw/d.

[5] MOE = NOAEL/PDR, where the short-term incidental oral NOAEL = 6.3 mg/kg/d

The MOEs calculated for incidental ingestion exposures by a toddler, as a result of the registered lawn renovation use, are greater than 300 and do not exceed HED's level on concern, separately.

Aggregate Toddler Exposure: The short-term dermal and short-term incidental oral exposure estimates were combined since the same toxicological endpoint was selected for each (HED's level of concern is for combined MOEs <300). HED's ExpoSAC policy directs assessors to aggregate the risk estimates for the hand-to-mouth ingestion, object-to-mouth ingestion, soil ingestion, and dermal exposures by a toddler, since it may be possible for a toddler to perform all of these incidental ingestion activities and receive dermal exposure from a treated lawn in a single day. Table 10 presents the aggregate risk of the combination of the short-term incidental ingestion and dermal exposures.

Table 10: Aggregate Residential Exposure and Risk Estimate for Short-term Incidental Ingestion and Dermal Exposures by Toddlers following Application of Glufosinate Ammonium for Lawn Renovation

Exposure	Average Daily Dose (ADD; mg/kg/day)	Short-term MOE
hand-to-mouth ingestion	0.0203	310
object-to-mouth ingestion	0.00508	1,200
soil ingestion	6.8×10^{-5}	93,000
post-application dermal exposure	0.265	**24**
Aggregate toddler residential exposure and risk[1]	0.290	**22**

The short-term aggregate dermal and ingestion MOE for toddlers, as a result of the lawn renovation use, exceed HED's level of concern (MOEs <300; MOE=22)

5.0 Aggregate Exposure and Risk Assessment

HED conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Glufosinate ammonium is registered for lawn renovation and spot treatment around trees, shrubs, fences, walks, patios, driveways, sidewalks, and flower beds. These registered residential uses result in short-term dermal and inhalation exposures. Since the same toxicological endpoints were selected for oral, dermal, and inhalation routes of exposure, aggregate risk assessments were conducted for acute (food and water), short-term (food, water, dermal, and inhalation), and chronic (food and water) exposures. Since HED does not have ground and surface water monitoring data to calculate quantitative chronic aggregate exposures, DWLOCs were calculated. The DWLOC is the theoretical upper limit of a chemical's concentration in drinking water that will result in aggregate exposures less than HED's level of concern. DWLOC values are not regulatory standards for drinking water. The DWLOC is used as a point of comparison against model estimates of a pesticide's concentration in water and were calculated using the following default body weights and drinking water consumption figures: 70kg/2L (adult male), 60kg/2L (adult female) and 10kg/1L (infant/child).

The EECs generated by the interim rice model represent the concentration of the residues of concern in rice paddy water on the day of application. The only environmental fate parameter considered in the interim rice model is soil:water partitioning (pesticide management practices, degradation, and dilution when the paddy water is released are not considered). As the water leaves the rice paddy, it is expected that glufosinate ammonium will be diluted by other water sources and photolysis will occur to break down the glufosinate ammonium compound. Additionally, rice paddies are not a direct source of drinking water. For the above reasons, estimate of residues in drinking water originating from surface water sources were generated using the FIRST model. Only the FIRST and SCIGROW EECs were used in the aggregate risk assessments.

Acute Aggregate Exposure Assessment: The acute aggregate risk assessment considers exposure from food and water. Residential exposures are not included since the acute aggregate risk assessment assumes high end exposure for food and water and HED concluded that it is unlikely that residential exposure will occur at the same time as high end food and water exposures. The acute dietary exposure analysis for females 13 - 50 years old (no acute dietary endpoint was identified for the general US population including infants and children) assumed tolerance level residues, DEEM™ default processing factors, and 100% crop treated for all registered and proposed commodities (Tier 1 analysis). The resulting exposure estimate for females 13-50 years old was less than HED's level of concern (<100% aPAD). As the water leaves the rice paddy, it is expected that glufosinate ammonium will be diluted by other water sources and photolysis will occur to break down the glufosinate ammonium compound. Additionally, rice paddies are not a direct source of drinking water. For the above reasons, estimate of residues in drinking water originating from surface water sources were generated using the FIRST model. Only the FIRST and SCIGROW EECs were used in the aggregate risk assessments. Excluding the rice interim model surface EECs, the surface and ground water EECs generated by EFED are less than HED's DWLOC (see Table 11). Acute aggregate exposure to glufosinate ammonium, as a result of all registered and proposed uses, is below HED's level of concern.

Table 11: Acute Aggregate Exposure

Population Subgroup	aPAD mg/kg/day	Food Exp mg/kg/day	Max Water Exp[1] mg/kg/day	Surface Water EEC[2] µg/l	Ground Water EEC[2] µg/l	DWLOC[3] µg/l
Females (13-50 years old)	0.021	0.007	0.014000	356	0.83	420

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - food exposure (mg/kg/day)

[2] EECs generated using the FIRST and SCIGROW models assuming 3 applications at 1.5 lbs ai/acre (registered apple grape and tree nut application scenario)

[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

Short-Term Aggregate Exposure Assessment: Since the short-term dermal, inhalation, and oral exposures can be aggregated (same toxicity endpoints), the short-term aggregate exposure assessments considered exposure from food, water, and residential sources. Since the HIARC identified different acceptable MOEs for residential dermal (acceptable MOE >300) and inhalation (acceptable MOE >3000) exposures, the aggregate assessment will use the ARI approach (HED's level of concern is for ARIs <1). The registered lawn renovation use resulted in an unacceptable short-term incidental oral and/or short-term dermal exposures for adults and children and, therefore, short-term aggregate exposure exceeds HED's level of concern. If the petitioner decides to revoke the lawn renovation use, then the following discussion concerning short-term aggregate exposure assessment is applicable (residential exposure from registered spot treatment use). The registered spot treatment use is expected to result in residential exposure to only adults. Therefore, short-term aggregate assessments were not conducted for infants and children.

HED uses average food (3-day; chronic estimates) and water exposure estimates when conducting short-term aggregate exposure assessments. Short-term exposure has been defined as from 1- 30 days and HED has concluded that average exposures to food and water will more accurately reflect actual exposure over these time periods than will high end exposures. The chronic dietary assessment assumed tolerance level residues, DEEM™ default processing factors, and 3-year weighted average percent crop treated information for apple, canola, corn, and grape commodities (100% crop treated assumed for the remaining crops). The resulting exposure estimates were less than HED's level of concern for the general US population and all population subgroups (<100% PAD). The residential dermal and inhalation exposure estimates were conducted using the draft residential SOPs and the resulting exposures were less than HED's level of concern. As the water leaves the rice paddy, it is expected that glufosinate ammonium will be diluted by other water sources and photolysis will occur to break down the glufosinate ammonium compound. Additionally, rice paddies are not a direct source of drinking water. For the above reasons, estimate of residues in drinking water originating from surface water sources were generated using the FIRST model. Only the FIRST and SCIGROW EECs were used in the aggregate risk assessments. (see beginning of section 5.0 for further information). Excluding the rice interim model surface EECs, the surface and ground water EECs generated by EFED are less than HED's DWLOC (for all population subgroups; see Table 12. Short-term aggregate exposure to glufosinate ammonium, as a result of all registered and proposed uses, is below HED's level of concern.

Table 12: Short-Term Aggregate Exposure

	ARI Food[1]	ARI dermal[1]	ARI inhalation[1]	Aggregate ARI[2]	ARI water[3]	MOE water[4]	Allowable water exposure[5] (mg/kg/day)	Ground Water EEC[6] (µg/l)	Surface Water EEC[6] (µg/l)	DWLOC[7] (µg/l)
spot treatment; low pressure hand wand										
U.S. pop - all seasons	5.39	1.43	253	1.13	8.85	2.66e+03	0.002372	0.86	56	83
Females (13-50 years old)	7.62	1.43	253	1.20	5.98	1.79e+03	0.003510	0.86	56	120
Males (13-19 years old)	4.88	1.43	253	1.10	10.7	3.21e+03	0.001965	0.86	56	69
Males (20+ years old)	7.23	1.43	253	1.19	6.24	1.87e+03	0.003363	0.86	56	120
Seniors (55+ years old)	8.11	1.43	253	1.21	5.71	1.71e+03	0.003677	0.86	56	130

[1] $ARI = MOE_{calculated\ (i.e.,\ food,\ dermal,\ inhalation)} \div MOE_{acceptable}$

[2] $\text{Aggregate ARI} = 1 \div (1/ARI_{food} + 1/ARI_{dermal} + ARI_{inhalation})$

[3] $ARI_{water} = 1 \div (1 - (1/ARI_{food} + 1/ARI_{dermal} + ARI_{inhalation}))$

[4] $MOE_{water} = ARI_{water} \times \text{Target } MOE_{water}$

[5] Allowable Water Exposure = NOAEL ÷ MOE_{water}

[6] EECs generated using the FIRST and SCIGROW models assuming 3 applications at 1.5 lbs ai/acre (registered apple grape and tree nut application scenario)

[7] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{\left(\text{maximium water exposure (mg / kg / day)}\right) * \left(\text{body weight (kg)}\right) * \left(1000\ \mu g / mg\right)}{\text{water consumption (liter / day)}}$$

Chronic Aggregate Exposure Assessment: The chronic aggregate exposure assessment considered exposure from food and water (no chronic residential exposure anticipated). The chronic dietary assessment assumed tolerance level residues, DEEM™ default processing factors, and 3-year weighted average percent crop treated information for apple, canola, corn, and grape commodities (100% crop treated assumed for the remaining crops). The resulting exposure estimates were less than HED's level of concern for the general US population and all population subgroups (<100% PAD). As the water leaves the rice paddy, it is expected that glufosinate ammonium will be diluted by other water sources and photolysis will occur to break down the glufosinate ammonium compound. Additionally, rice paddies are not a direct source of drinking water. For the above reasons, estimate of residues in drinking water originating from surface water sources were generated using the FIRST model. Only the FIRST and SCIGROW EECs were used in the aggregate risk assessments. Excluding the rice interim model surface EECs, the surface and ground water EECs generated by EFED are less than HED's DWLOCs (see Table 13). Chronic aggregate exposure to glufosinate ammonium, as a result of all registered and proposed uses, is below HED's level of concern.

Table 13: Chronic Aggregate Exposure

Population Subgroup	cPAD mg/kg/day	Food Exp mg/kg/day	Max Water Exp[1] mg/kg/day	Surface Water EEC[2] ppb	Ground Water EEC[2] ppb	DWLOC[3] ppb
U.S. pop - all seasons	0.02	0.003894	0.016106	56	0.86	560
All Infants (<1 year old)	0.02	0.009391	0.010609	56	0.86	110
Children (1-6 years old)	0.02	0.009522	0.010478	56	0.86	100
Children (7-12 years old)	0.02	0.006203	0.013797	56	0.86	480
Females (13-50 years old)	0.02	0.002756	0.017244	56	0.86	520
Males (13-19 years old)	0.02	0.004301	0.015699	56	0.86	550
Males (20+ years old)	0.02	0.002903	0.017097	56	0.86	600
Seniors (55+ years old)	0.02	0.002589	0.017411	56	0.86	610

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - food exposure (mg/kg/day)

[2] EECs generated using the FIRST and SCIGROW models assuming 3 applications at 1.5 lbs ai/acre (registered apple grape and tree nut application scenario)

[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

6.0 Cumulative

The FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this registration because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of glufosinate ammonium. For purposes of this registration, EPA has assumed that glufosinate ammonium does not have a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether glufosinate ammonium shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for glufosinate ammonium need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with glufosinate ammonium, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at: http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf. In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0 Occupational Exposure and Risk Assessment

Pesticide handlers supporting and conducting applications to cotton, rice, and bushberry crops are anticipated to have short-term dermal and inhalation exposures. Intermediate exposures are not anticipated for commercial applicators treating rice and cotton crops given the 10 to 14 day RTI on the proposed label. Workers entering fields following applications have the potential for short-term dermal exposures. The following PPE is specified on the respective proposed labels handlers:

- Liberty® label (cotton and rice): coveralls worn over short-sleeved shirt, short pants, chemical-resistant gloves, chemical-resistant shoes with socks, protective eyewear, plus chemical-resistant apron when mixing/loading and cleaning equipment.
- Rely® label (bushberry): long-sleeved shirt, long pants, chemical-resistant gloves, and shoes with socks and protective eyewear.

7.1 Handler Exposure Assumptions and Risk Assessment

No chemical specific data were available to assess potential exposures to workers from the proposed uses. Therefore, this exposure assessment was conducted using data available in the Pesticide Handler's Exposure Database (PHED) Surrogate Table (v1.1., 1998). The rationale for the use of PHED data in occupational exposure risk assessment is outlined in ExpoSAC Policy 007 (Jan. 28, 1999). This assessment presents dermal and inhalation exposure and risk assessments for:

- Mixer/loader supporting aerial and ground applications; *Note:* Exposure and risk estimates are presented for both cotton and rice crops for this scenario.
- Aerial applicator; *Note:* Exposure and risk estimates are presented for cotton applicators only, since the application rate is higher for cotton vs. rice crops.
- Flagger supporting aerial application (although most applicators use global positioning system [GPS] units in place of human flaggers).
- Groundboom applicator (see mixer/loader/applicator [MLAP] discussion below).
- MLAP, backpack applicator for spot treatment (bushberries only).

Table 14 lists the assumptions used in the handler exposure assessment and the corresponding dermal and inhalation MOEs. Note that per HED policy, baseline PPE (single layer of clothing, no gloves, and no respirator) was used to estimate handler exposures, where possible. However, Liberty® label requires handlers to wear chemical-resistant gloves and coveralls, and the Rely® label requires handlers to wear chemical-resistant gloves, so these PPE levels were also assessed, where appropriate. Note that although the Liberty® label specifies that handlers were a chemical-resistant apron, HED does not add a protection factor for this additional layer as aprons are considered to mitigate gross spills and provide for general hygiene. Additionally, in cases where the inhalation MOEs exceed HED's level of concern, handler exposure was also assessed using a dust-mist respirator, which provides an 80% reduction in inhalation exposure per PHED.

Note on MLAPs: HED's draft policy (Exposure SAC, 29-MAR-2000) recommends that exposure and risk estimates for mixer/loaders and applicators for tractor drawn equipment remain separate unless specific and/or crop information exists to warrant the combining of the two estimates. Therefore, exposure and risk estimates for a combined MLAP groundboom scenario are not presented in Table 14. Separate exposure and risk estimates are presented for a mixer/loader supporting ground applications and a groundboom applicator. The HIARC concluded that the dermal and inhalation exposures can be aggregated. Since the target MOEs for residential dermal (>300) and inhalation (>3000) exposures are different, an ARI approach was used to aggregate dermal and inhalation exposures (ARIs greater than 1 do not exceed HED's level of

concern; see HED's *Guidance for Performing Aggregate Exposure and Risk Assessments*, 29-Oct-1999).

Table 14: Handler Exposure and Risk Assessment for Proposed Uses of Glufosinate Ammonium

Exposure Scenario	Unit Exposure[1] (mg/lb ai handled)	AR[2] (lb ai/acre, unless specified)	Acres/d[3] (unless specified)	Average Daily Dose[4] (mg/kg bw/d)	Short-term Dermal MOE[5]	Short-term Inhalation MOE[5,8]	Short-term ARI[6]
Mixer/loader (M/L) liquid, open pour, supporting aerial application	dermal: S/L w/o gloves[7]: 2.9 (HC) S/L w/gloves[7]: 0.023 (HC) closed M/L: 0.0086 (HC)	**0.52 (cotton)**	1,200	dermal: w/o gloves: 15.1 w/gloves + coveralls: 0.091 closed sys: 0.0447	w/o gloves: 0.41 w/gloves + coveralls: 69 closed sys: 140	w/o resp: 500 w/resp[8]: 2,500 closed sys: 7,300	w/o gloves & resp.: **0.0041** w/gloves + coveralls & resp.: **0.54** closed sys[9]: 1.2
	inhalation: 0.0012 (HC) closed M/L: 8.3×10^{-5} (HC)			inhalation: 0.0125 w/resp[8]: 0.0025 closed sys: 0.000863			
M/L: liquid, open pour, supporting ground application	dermal: S/L w/o gloves: 2.9 (HC) S/L w/gloves: 0.023 (HC)		200	dermal: w/o gloves: 2.51 w/gloves: 0.0199	w/o gloves: 2.5 w/gloves: 320	w/o resp: 3,000	w/o gloves: **0.025** w/gloves: 1.5
	inhalation: 0.0012 (HC)			inhalation: 0.00208			
Applicator: aerial, enclosed cockpit, liquid formulation	dermal: S/L w/o gloves: 0.0050 (MC)		1,200	dermal: w/o gloves: 0.0260	w/o gloves: 240	8,900	w/o gloves: 1.9
	inhalation: 0.000068 (MC)			inhalation: 0.000707			
Flagger supporting aerial application	dermal: S/L w/o gloves: 0.011 (HC)		350	dermal: w/o gloves: 0.0167	w/o gloves: 380	5,900	w/o gloves: 2.3
	inhalation: 0.00035 (HC)			inhalation: 0.00106			
Applicator: groundboom, open cab	dermal: S/L w/o gloves: 0.014(HC)		200	dermal: w/o gloves: 0.0121	w/o gloves: 520	4,900	w/o gloves: 2.5
	inhalation: 0.00074 (HC)			inhalation: 0.00128			
M/L: liquid, open pour, supporting groundboom application	dermal: S/L w/o gloves: 2.9 (HC) S/L w/gloves: 0.023 (HC)	**1.5 (bushberry)**	80	dermal: w/o gloves: 2.9 w/gloves: 0.023	w/o gloves: 2.2 w/gloves: 270	2,600	-w/o gloves: **0.0086** - w/gloves: 1.3
	inhalation: 0.0012 (HC)			inhalation: 0.0024			

Exposure Scenario	Unit Exposure[1] (mg/lb ai handled)	AR[2] (lb ai/acre, unless specified)	Acres/d[3] (unless specified)	Average Daily Dose[4] (mg/kg bw/d)	Short-term Dermal MOE[5]	Short-term Inhalation MOE[5,8]	Short-term ARI[6]
Applicator: groundboom, open cab	dermal: S/L w/o gloves: 0.014 (HC) inhalation: 0.00074 (HC)		80	dermal: w/o gloves: 0.014 inhalation: 0.0015	w/o gloves: 450	4,200	w/o gloves: 2.2
MLAP: backpack sprayer, bushberry	dermal: S/L w/gloves: 2.5 (LC); no w/o gloves data available inhalation: 0.030 (LC)	**0.0312 lb ai/gal water (bushberry)**	40 gal/d	dermal: w/gloves: 0.0260 inhalation: 0.000625	w/gloves: 240	10,000	w/gloves: 1.9
M/L: liquid, open pour, supporting aerial application	dermal: S/L w/o gloves: 2.9 (HC) S/L w/gloves: 0.023 (HC) closed M/L: 0.0086 (HC)[9] inhalation: 0.0012 (HC) closed M/L: 8.3 x 10^{-5} (HC)	**0.44 (rice)**	1,200	dermal: w/o gloves: 12.8 w/gloves + coveralls: 0.077 closed sys: 0.0378 inhalation: 0.0106 w/resp.: 0.00212 closed sys: 0.000730	w/o gloves: 0.49 w/gloves: 82 closed sys: 170	w/o resp: 600 w/resp: 3,000 closed sys: 8,600	w/o gloves & resp.: **0.0049** w/gloves + coveralls & resp.: **0.64** closed sys: 1.4
M/L: liquid, open pour, supporting ground application	dermal: S/L w/o gloves: 2.9 (HC) S/L w/gloves: 0.023 (HC) inhalation: 0.0012 (HC)		200	dermal: w/o gloves: 2.13 w/gloves: 0.0169 inhalation: 0.00176	w/o gloves: 3.0 w/gloves: 370	w/o resp: 3,600	w/o gloves & resp.: **0.030** w/gloves : 1.8

[1] Source: Pesticide Handlers Exposure Database (PHED) Surrogate Exposure Table (v1.1., 1998). (HC) = high confidence data; (MC) = medium confidence data; (LC) = low confidence data. For MLAP backpack sprayer, the combined PHED scenario (Scenario No. 34) was used per ExpoSAC policy.

[2] AR = Maximum application rate. Note: For MLAP backpack sprayer, application rate was based on: 4 fl. oz. Rely®/gal water x 1lb ai/gal x 1 gal/128 fl oz = 0.0312 lb ai/gal mix; 40 gal mix/d applied x 0.0312 lb ai/mix = 1.25 lb ai/d.

[3] Daily amount handled for backpack sprayer from Exposure SAC Policy No. 9, July 5, 2000.

[4] ADD = Unit exposure(mg/lb ai) x AR x Acres/Day x 1/BW (60 kg used for dermal and inhalation exposure assessments. Per HIARC, since a NOAEL was selected from developmental toxicity study, a 60 kg body weight should be used in the calculating the human equivalent dose.) x 50% dermal absorption and100% inhalation absorption rate to convert to oral equivalents per HIARC.

[5] MOE = NOAEL/ADD; short-term dermal and inhalation NOAEL =6.3 mg/kg/day; HED's level of concern for dermal exposures is for MOEs <100 (occupational) and for inhalation exposures is for MOEs <1000.

[6] ARI = Aggregate Risk Index; 1/((1/(calculated dermal MOE/target MOE (100)) + (1/(calculated inhalation MOE/target MOE (1,000))). Target ARI is 1.

[7] S/L w/o gloves: single layer of clothing without gloves; S/L w/gloves: single layer of clothing with gloves.
[8] The addition of a dust/mist respirator as PPE for the handler provides an 80% reduction in inhalation exposure per PHED (resp = respirator).
[9] See discussion on closed mixing/loading in text below.

A discussion of occupational handler assessment is provided below, and is broken down by PPE level, particularly for mixer/loaders supporting applications to cotton and rice crops as the risk estimates for these exposure scenarios exceeded HED's level of concern both at the baseline level (single layer, no gloves) and at additional levels of protection (gloves, and respirator) for aerial applications.

At Baseline Level: Cotton, Rice and Bushberry: The following exposure scenarios have a total short-term ARI less than 1 (exceed HED's level of concern; 0.0041) at the baseline level:

- Mixer/loader supporting aerial and ground applications on cotton and rice.
- Mixer/loader supporting ground applications on bushberry.

With Label PPE plus Dust-Mist Respirator for Mixer/Loaders Supporting Aerial Applications to Cotton and Rice: The mixer/loader supporting aerial applications on cotton and rice scenario has a total ARI less than 1 when handlers wear PPE specified on the label (ARIs = 0.54 and 0.64, respectively).

Note that the proposed label requires that handlers performing mixing/loading wear a chemical-resistant apron, so although HED does not quantify the mitigation potential of this additional layer of clothing, HED anticipates that some additional dermal protection is provided by the apron during mixing/loading activities.

With Closed Mixing/Loading System for Mixer/Loaders Supporting Aerial Applications to Cotton and Rice: Closed mixing/loading systems typically comprise "lock and load" systems whereby handlers have minimal direct contact with the formulation and the mixed spray. Dermal and inhalation unit exposures for handlers performing closed mixing/loading are included in PHED and were used to estimate handler exposures for this scenario. The resulting ARIs for the mixer/loaders supporting aerial applications to cotton and rice are 1.2 and 1.4, respectively, when closed mixing/loading systems are used. These ARIs do not exceed HED's level of concern.

With Label PPE for Mixer/Loaders Supporting Ground Applications to Cotton and Rice: With the addition of chemical-resistant gloves as required by the Liberty® label, the ARIs for mixer/loaders supporting ground applications is greater than 1 (ARI = 1.5 and 1.8., respectively) and do not exceed HED's level of concern.

With Label PPE for Mixer/Loaders Supporting Groundboom Applications to Bushberry: With the addition of chemical-resistant gloves as required by the Rely® label, the ARI for mixer/loaders supporting ground applications is greater than 1 (ARI = 1.3) and does not exceed HED's level of concern.

Therefore, the petitioner should submit a revised Section B indicating that for aerial application to cotton and rice only closed mixing/loading systems may be used.

7.2 Post-Application Exposure and Risk Assessment

Workers entering treated cotton, rice, and bushberry fields are anticipated to have short-term dermal exposures; post-application inhalation exposures are not anticipated given the vapor pressure of glufosinate ammonium technical is not determinable (physical state = crystalline powder). Anticipated cultural activities resulting in post-application exposures comprise irrigation and scouting in rice, cotton, and bushberry fields based on the following application timing/label instructions:

- For cotton applications, Liberty® may be applied from planting up to early bloom stage on tolerant cotton. For conventional cotton, a hooded sprayer is required to only control emerged weeds.
- For rice applications, Liberty® may be applied up to the 5-leaf stage with a second application up to the mid-tillering growth stage.
- For bushberry applications, Rely® should be applied as a directed spray to weeds so that the product does not contact the bushberry bushes as damage will occur.

Given the above application considerations, the anticipated cultural activities that would result in post-application exposures and the relevant transfer coefficients related to these activities are (source: ExpoSAC Policy No. 3.1, August 7, 2000):

- Scouting in rice and cotton crops with minimal foliage development: 100 cm^2/hr (MRID 426891). Note only minimal foliage contact is anticipated by workers entering treated areas based on the application timing instructions.

Post-application exposure by workers entering bushberry fields is anticipated to be considerably less than the exposure estimates for scouting in rice and cotton crops, since applications to bushberry are targeted to weeds and not the crop itself.

There are no chemical-specific, post-application exposure data available for glufosinate ammonium. As such, standard HED post-application assumptions were used to provide an estimate of post-application exposure risks to workers. Specifically, the residue transfer coefficients (TCs) used in this assessment are from an interim transfer coefficient policy developed by HED's ExpoSAC using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (ExpoSAC Policy No. 3.1). It is the intention of HED's Science Advisory Council for Exposure that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature. The following assumptions were used in worker post-application exposure assessment:

- Maximum application rate of 0.52 lb a.i./A on cotton (note that cotton has a higher maximum *per* application rate than rice).
- 20% of the maximum application rate are available as dislodgeable foliar residues (DFR) available on Day 0.
- TC of 100 cm^2/hour as discussed above.
- Work day of 8 hours.

In order to assess the potential post-application exposures, an estimate of dislodgeable foliar residues (DFR) on Day 0 was used, and this residue estimate is anticipated to represent the highest short-term post-

application exposure for the proposed use pattern (see Table 15 below):

Table 15: Post-Application Worker Exposure and Risk Assessments for Glufosinate Ammonium

Exposure Scenario	AR (lb a.i./A)	Transfer Coefficient (cm^2/hr)	DFR estimate[1] ($\mu g/cm^2$)	Average Daily Dose[2] (mg/kg bw/day)	Short-term Dermal MOE[3]
Cotton: scouting	0.52	100	1.17	0.00780	810

[1] Surrogate DFR on Day of Treatment = application rate (lb a.i./A) x 20% available as dislodgeable residue x 4.54E8 ug/lb x 2.47E-8 A/cm^2. Ex. calc = 1.5 lb ai/acre x 0.20 x 4.54E8 ug/lb x 2.47E-8 A/cm^2 = 3.36 $\mu g/cm^2$.

[2] ADD =DFR (ug/cm^2) x TC (cm^2/hr) x 8 hrs/day x 0.001 mg/ug x 1/ BW x 50% dermal absorption; BW= 60kg; Ex. calc. for cotton: ADD = 1.17 $\mu g/cm^2$ x 100 cm^2/hr x 8 hrs/day x 0.001 mg/ug x 1/60 kg x 0.50 = 0.00780 mg/kg/d.

[3] MOE = NOAEL/ ADD; short-term dermal NOAEL = 6.3 mg/kg bw/day. The level of concern is for MOEs <100.

The MOE for entering treated cotton fields is greater than 100 and do not exceed HED's level of concern. As discussed earlier, post-application exposure and risk estimates for workers entering treated rice and bushberry fields are anticipated to be lower than the MOE for cotton fields.

7.3 REI

The REI on the proposed labels is 12 hours. A 12-hour REI is appropriate under the Worker Protection Standard (WPS) based on an acute Toxicity Category III for the dermal, inhalation, and ocular routes of exposure for glufosinate ammonium.

7.4 Incidents

A total of 268 records were listed in HED's REFs database (search conducted 14-May-2002). The majority of these incidents were characterized as "unknown" probability or were related to crop damage or animal injury. Two records contained a reference to approximately 6 human cases related to skin effects (rashes, skin burns) related to the Liberty® end-use product (EPA Reg. No. 45639-187).

8.0 Actions Required by Petitioner - Data Gaps

8.1 Toxicology

- Comparative measurements of glutamine synthetase activity (brain, kidney and liver) in young and adult animals.
- A Developmental Neurotoxicity Study (DNT) in rats (previously required by HIARC).
- Repeat of Acute Neurotoxicity Study in rats with glufosinate ammonium (only) with adequate dosing as per the guideline. This study should also include measurements of glutamine synthetase activity (brain, kidney and liver).
- A 28-day inhalation toxicity study in rats with glutamine synthetase activity measurements in brain, kidney, liver and lung).
- Additional data are required to confirm that liver and kidney changes, observed in the absence of histopathological changes, are adaptive response and not an adverse effect. It should include kidney and liver function assays in addition to glutamine synthetase activity measurements and required routine parameters.

8.2 Residue Chemistry

- Revised Section B
- Revised Section F
- Blueberry field trial study conducted in Region 12 (n=1; including residue decline data)

8.3 Occupational/Residential

- Revised Section B (only closed mixing/loading systems may be used for aerial application to rice and cotton)
- The registered lawn renovation use resulted in short-term incidental oral exposure and/or short-term dermal exposure for adults and children greater than HED's level of concern. Therefore, short-term aggregate exposure to glufosinate ammonium will exceed HED's level of concern. HED recommends that the lawn renovation use be revoked.

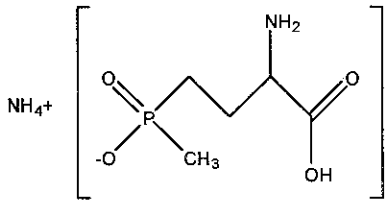
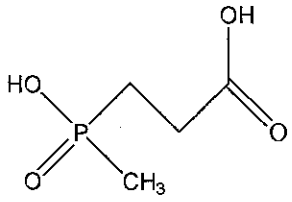
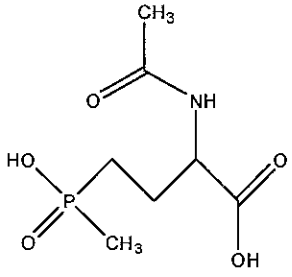
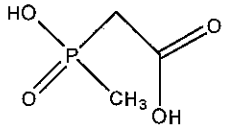
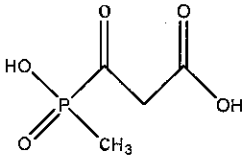
References

1. HIARC - TXR No. 0050900
2. FQPA SFC - TXR No.0050964
3. MARC - D282757, T. Bloem, 9-May-2002
4. residue chemistry - D271110, T. Bloem, 20-Jun-2002
5. occupational/residential exposure assessment - D284811, T. Swackhammer, 13-Aug-2002
6. DEEM™ analysis - D283555, T. Bloem, 25-Jul-2002
7. drinking water - D280453, J. Ravenscroft, 8-Aug-2002

attachment 1: structures

cc: T. Bloem (RAB1), PV Shah (RAB1), T. Swackhammer (RAB1)
RDI: RAB1 (7-Aug-2002)

Attachment 1: chemical structures

Chemical Name	Chemical Structure
glufosinate ammonium HOE 039866 CAS name - butonoic acid, (±)-2-amino-4-(hydroxymethylphosphinyl)-, monoammonium salt technical is a racemic mixture of the D and L isomers	
HOE 061517 IUPAC name - 3-methylphosphinico-propionic acid CAS name - 3- (hydroxymethylphosphinyl)-propionic acid	
HOE 099730 IUPAC name - L-2-acetamido-4-methylphosphinico-butanoic acid CAS name - L-2-(acetylamino)-4-(hydroxymethyl-phosphinyl)butanoic acid common name: L-N-acetyl-glufosinate the tolerance expression will include both the D and L isomers; enantiomeric form in plants, livestock, and water is unknown (analytical methods did not distinguish D and L enatiomers)	
HOE 064619 2-methylphosphinico-acetic acid	
HOE 086486	

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050820

Chemical:	**Butanoic acid, 2-amino-4-(hydroxy-methyl**
PC Code:	**128850**
HED File Code	**14000 Risk Reviews**
Memo Date:	**08/09/2002**
File ID:	***DPD274674; DPD274675; DPD280452***
Accession Number:	**412-03-0016**

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